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Mechanisms of Experience-dependent Prevention of Plasticity in Visual Circuits

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MECHANISMS OF EXPERIENCE-DEPENDENT PREVENTION OF PLASTICITY IN VISUAL
CIRCUITS

by

TIMOTHY S. BALMER

Under the Direction of Sarah L. Pallas

ABSTRACT

Development of brain function is instructed by both genetically-determined processes (nature) and environmental stimuli (nurture). The relative importance of nature and nurture is a major question in developmental neurobiology. In this dissertation, I investigated the role of visual experience in the development and plasticity of the visual pathway. Each neuron that receives visual input responds to a specific area of the visual field- their receptive field (RF). Developmental refinement reduces RF size and underlies visual acuity, which is important for survival. By rearing Syrian hamsters (*Mesocricetus auratus*) in constant darkness (dark rearing, DR) from birth, I investigated the role of visual experience in RF refinement and plasticity. Previous work in this lab has shown that developmental refinement of RFs occurs in the absence of visual experience in the superior colliculus (SC), but that RFs unrefine and thus enlarge in adulthood during chronic DR. Using an *in vivo* electrophysiological approach, I show that, contrary to a widely held view, visual experience is not necessary for refinement of RFs in primary visual cortex (V1). In both SC and V1, RFs refine by postnatal day (P) 60, but enlarge by P90 with chronic DR.

One week of visual experience was sufficient to prevent RF enlargement in SC and V1. How normal sensory experience prevents plasticity in mature circuits is not well understood. Using an *in vitro* electrophysiological approach, I demonstrated that GABAergic inhibition is reduced in DR SC, which in turn affects short-term (but not long-term) synaptic plasticity. The level of GABA_BR-mediated short-term synaptic depression (STD) that occurs during high-frequency afferent stimulation, such as occurs during vision, is reduced by DR. Using a computational model of RF size, I propose that, in addition to the effect of reduced inhibition, reduced STD of excitation could contribute to enlarged RFs. This work provides insight into mechanisms of development and plasticity of the nervous system. How plasticity is restricted in mature circuits is of fundamental importance in neuroscience and could instruct therapies to prevent maladaptive plasticity in disease and to enhance recovery of function in adults.

INDEX WORDS: Superior colliculus, Visual cortex, Adult plasticity, Receptive field, Inhibitory plasticity, Rodent, Critical period, Visual deprivation

MECHANISMS OF EXPERIENCE-DEPENDENT PREVENTION OF PLASTICITY IN VISUAL
CIRCUITS

by

TIMOTHY S. BALMER

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2014

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1 INTRODUCTION

The ability of the nervous system to sense, perceive and respond to the environment is astounding. The underlying anatomical, synaptic, molecular and computational complexity of the brain is unlike anything else in nature. Development of such a structure requires both genetically-determined intrinsic cellular processes (nature) and sensory-evoked environmental input (nurture). The relative importance of nature and nurture in the development of the nervous system is a question of major importance to basic developmental neurobiology.

In systems neuroscience, a widely held view is that sensory experience contributes to the development of sensory function, and that without such experience, proper development cannot occur. In Chapter 2, I challenge this view with experimental evidence indicating that development occurs in the absence of experience in both midbrain superior colliculus (SC) and primary visual cortex (V1) of Syrian hamsters.

Once circuits reach their mature state of refinement, they are stabilized. This prevents regression from the mature state, but also limits recovery from brain injury in adults. In many cases, modality specific experience during a critical period in development is what prevents adult plasticity. For example, dark rearing (DR) prolongs the critical period for ocular dominance plasticity in V1, but visual experience normally closes the critical period, stabilizing circuits and preventing adult plasticity (Cynader and Mitchell, 1980).

It is unclear what mechanisms underlie this experience-dependent prevention of plasticity, but inhibition is a strong candidate because its maturation is regulated in part by experience (Morales et al., 2002) and shapes sensory responses directly (Carrasco et al., 2011). In addition, dysregulation of inhibition could disrupt sensory processing by altering long- or short-term synaptic plasticity (Kirkwood and Bear, 1994; Fagiolini and Hensch, 2000). In Chapter 3, I provide support for a physiological mechanism of experience-dependent maintenance and plasticity of visual function in SC.

1.1 Nervous system development and plasticity

Initial development of the nervous system necessarily depends on activity-independent intrinsic genetic instructions before neurons are able to fire action potentials and before synapses form. These processes include neuronal differentiation, migration, and projection of axons to their target areas, and are extensively reviewed elsewhere (Tessier-Lavigne and Goodman, 1996; Kanold and Luhmann, 2010; Kiecker and Lumsden, 2012; Pfaff and Shaham, 2013).

Once circuits are initially wired, fine tuning occurs, and both spontaneously-generated and sensory-evoked activity begins to play important roles. Sensory-evoked activity is necessary during critical periods in development to establish and fine tune physiological properties. One of these properties is the receptive field (RF). A RF is the area of the visual field to which each neuron responds. A crucial and often overlooked aspect of visual system development is the refinement of receptive fields (RFs). Because RF size contributes directly to visual acuity, it may be especially critical for survival for both predator and prey animals. In this section, I review the role of experience-independent and experience-dependent development of visual circuits, followed by proposed mechanisms of experience-dependent prevention of plasticity in adulthood.

1.1.1 Visual system as a model of nervous system development and plasticity

The visual system is useful for understanding nervous system development in general. The visual system exhibits both spontaneously-generated and visually-evoked neural activity. These forms of activity can be manipulated by surgery, pharmacological agents, and modification of the rearing environment. Indeed, since the first experiments on visual cortical development in the 1960s, the role of spontaneously-generated and sensory-evoked activity in visual system development and plasticity has been an active area of study.

1.1.2 General organization of the mammalian subcortical and cortical visual systems

Transduction of visual stimuli starts in the retina, a layered network of neurons that detects luminance across the visual field. Visual processing in the retina occurs through lateral inhibition, motion decoding, and color detection (Kaneko, 1979; Daw et al., 1989; Marr, 2010). The output pathway from the retina is the optic nerve, which is composed of the axons of the retinal ganglion cells (RGCs). The optic nerve innervates SC and the lateral geniculate nucleus of the thalamus (LGN). These two retinal targets both interact and function in parallel (Schneider, 1969).

The SC is a sensorimotor midbrain area that receives input from all sensory modalities and is vital for orienting the eyes, head, trunk, and ears to stimuli in the environment (Mort et al., 1980; Stein, 1984; Isa, 2002). The superficial (dorsal) layers of the SC receive and process visual input. The optic tract (the term for the optic nerve within the CNS) enters anterior SC into the optic layer (stratum opticum) and innervates the superficial gray layer in a topographically organized manner, as described below. A corticocollicular projection from V1 (primary visual cortex, *aka* Area 17) also enters the SC from the optic layer (Powell, 1976; Rhoades and Chalupa, 1978c), in topographic register with the retinotopic map (Triplett et al., 2009). The deeper layers of SC receive inputs from the other sensory modalities in addition to inputs from parietal cortex and basal ganglia. Both superficial and deep layers of SC project to the brainstem in order to control motor output and to initiate movement of the head toward a stimulus.

LGN also receives direct input from the RGCs and acts as a relay, sending the signals to V1. The tuning properties of LGN neurons are similar to those of the RGCs themselves, which suggests that little transformation of stimulus representation occurs in LGN (Wiesel and Hubel, 1966). The inputs from the two eyes remain segregated in LGN in primates and carnivores but not in rodents.

V1 is the first cortical area that receives visual input and is where properties such as orientation tuning and binocular responses are first observed. LGN innervates layer 4 of V1. In general, layer 4 neurons project to layers 2 and 3 (referred to as layer 2/3 in rodents and carnivores), which in turn send signals horizontally within the same cortical area and to other cortical areas, as well as vertically to layer 5 and 6. Layer 5 sends long-range afferents to the SC. Layer 6 sends output back to LGN. These

microcircuits between and within the layers of V1 are complex, with cell-type specific interactions (Maffei and Turrigiano, 2008), and are an active area of research.

Cells in layers 2 and 3 are the first to receive convergent input from both eyes. These binocularly responsive neurons underlie stereopsis and are the neurons of interest in most studies of ocular dominance plasticity (although other layers are also studied and appear to be affected differently by visual experience (Kirkwood et al., 1995; Daw et al., 2004; Tagawa et al., 2005)). There are species differences in the extent to which V1 neurons receive binocular inputs. Due to their laterally-placed eyes, V1 in most rodents receives the majority of its input from the contralateral eye and has only a very small portion that responds binocularly. Primates and carnivores, on the other hand, have a different organization. Many cells in primate V1 respond to both eyes, and the neurons exhibiting dominance of the input of one eye over the other are organized in columns or stripes (Hubel and Wiesel, 1968). Species differences in binocularity are not surprising, given the difference in visual field overlap of the two eyes in animals with forward-facing vs side-facing eyes.

In mice, V1 projects to dozens other cortical areas for further processing (Wang et al., 2012). In general, the projections can be categorized into dorsal and ventral streams that process the location and identity of objects, respectively (Mishkin and Ungerleider, 1982; Livingstone and Hubel, 1987; Goodale and Milner, 1992). Higher visual areas appear to be more plastic in adulthood than primary sensory areas, and are the focus of exciting work, especially in primates (Sasaki et al., 2010). This dissertation focuses on primary visual areas and will not discuss higher visual areas in detail.

1.1.3 Activity-independent factors in visual system development

The visual information captured by the retina is represented in SC, LGN, and V1 such that neighboring sensory neurons in the eye project to neighboring neurons in each structure, forming a two-dimensional retinotopic map of visual space. The retinocollicular projection has been widely used to investigate the role of molecular guidance cues in the formation of retinotopic maps. Retinotopic maps

form before birth in many mammals, indicating that visually-evoked activity is not necessary for their initial patterning.

The first experiments suggesting that RGC afferents from the eye are able to find the appropriate CNS target based on molecular interactions came from work in amphibian tectum, the non-mammalian homolog to SC. Cutting the optic nerve of a frog and surgically rotating the eye caused RGC axons to regenerate to the part of the tectum that normally represented the same part of the retina, irrespective of the abnormal positioning of the retina (Sperry, 1944) or whether the entire retina was present (Sperry, 1963).

The RGC axons in rodents project via the optic nerve/tract into anterior SC and initially innervate a large target area, projecting to the caudal edge of the SC (Simon and O'Leary, 1992). Repulsive interactions between EphA receptors on the developing axons and ephrinA ligands expressed on the surface of SC cells mediate growth cone retraction and back-branching at the correct topographic location. Opposing molecular gradients of these receptors and ligands force high EphA-expressing axons from temporal retina to remain in rostral SC where low levels of ephrinAs are expressed (McLaughlin et al., 2003a). Low EphA-expressing axons from nasal retina on the other hand, are able to continue through the rostral SC and into the caudal portion of SC with its high levels of ephrinAs, where they remain because they are less sensitive to the repulsive interaction (Udin and Fawcett, 1988; Simon and O'Leary, 1992; Brown et al., 2000; Feldheim and O'Leary, 2010; Triplett, 2014). Transgenic mice lacking ephrinAs have profoundly disordered retinotopic maps (Frisén et al., 1998; Feldheim et al., 2000). The mediolateral axis of SC depends on somewhat similar interactions between opposing ephrinB and EphB receptor gradients (Hindges et al., 2002). Retinotopic mapping of SC is an example of activity-independent development, because even when activity is blocked the retinotopic map develops, although it is less precise (Meyer, 1983; Harris, 1984; Thompson and Holt, 1989).

Most aspects of retinal development proceed in the absence of sensory input and in the absence of neural activity (Sun et al., 2011; Wei et al., 2011), consistent with the general pattern that lower visual areas rely on activity-independent development to a greater extent than do higher visual areas.

1.1.4 Activity-dependent factors in visual system development

Once a rough retinotopic map is formed, guided largely by molecular interactions, fine tuning of the arbors to their precise locations and arbor shape/size requires neural activity. Retinotopic maps in SC, LGN, and V1 develop before visually evoked activity is possible (Jeffery, 1985; Chalupa and Snider, 1998; Cang et al., 2005) and thus rely on spontaneous activity. Refinement of the retinocollicular arbors to a small terminal zone in the SC is essential for the development of refined RFs, high acuity perception, and other visual properties. This refinement process could occur through spontaneous or sensory-evoked activity, via instructive and/or permissive mechanisms (Katz and Shatz, 1996).

1.1.4.1 Spontaneously-generated activity

Spontaneous activity exists at many levels of the visual system including the retina (Firth et al., 2005), LGN (Weliky and Katz, 1999) and V1 (Chiu and Weliky, 2001). Spontaneous waves of activity propagate across the retina during early postnatal development. The first stage is generated by gap junctions and ends around the time of birth in rodents and ferrets (Firth et al., 2005). This is followed by retinal waves generated by acetylcholine released by starburst amacrine cells. These waves are propagated via nAChRs across the retina, and through the optic nerve to the SC and LGN (Galli and Maffei, 1988; Wong et al., 1993; Feller et al., 1996). About a week after birth these waves subside and are replaced with waves mediated by glutamate released from bipolar cells (Wong et al., 2000) that activate AMPARs and NMDARs on RGCs. The glutamatergic retinal waves cease a few days after eye opening, but it is important to note that visual experience does not cause them to end and that DR does not prolong them (Demas et al., 2003). Spontaneous activity persists throughout life, but the activity is not structured in propagating waves.

Experiments using various approaches to disrupt patterned spontaneous activity have shown that retinal waves are necessary for normal development of the visual system. The most extreme approach to disrupting retinal activity is by eye removal (enucleation). This causes the optic nerve to degenerate, so

retinocollicular afferents are lost and topographic maps cannot form. However, thalamocortical afferents from LGN remain, and remarkably, some normal development occurs (Crowley and Katz, 1999), in addition to miswiring (Rakic et al., 1991), perhaps guided by spontaneous activity that occurs in LGN itself (Weliky and Katz, 1999; Weliky, 2000).

A somewhat less extreme but still profound manipulation of spontaneous and evoked activity is the pharmacological inactivation of the retina by intraocular tetrodotoxin (TTX) injection, which blocks voltage-dependent Na⁺ channels and prevents spiking. Silencing RGC activity in this way causes retinocollicular map miswiring, although crude topographic maps do form (Meyer, 1983; Thompson and Holt, 1989). The normal eye specific segregation of the retinogeniculate axons in LGN is also disrupted by activity blockade with TTX (Shatz and Stryker, 1988; Sretavan et al., 1988). Thalamocortical and corticothalamic innervation that occurs before birth is also disrupted by ventricular infusion of TTX, indicating a role- in addition to molecular guidance (Molnar et al., 2012)- for spontaneous activity in the initial formation (Stryker and Harris, 1986) and refinement of those projections (Antonini and Stryker, 1993; Catalano and Shatz, 1998). However, TTX prevents all neural activity, including sensory-evoked activity that occurs after birth, which makes interpretation of these results difficult. Specifically, activity blockade experiments are not able to refute the hypothesis that sensory-evoked activity, rather than spontaneous activity, is necessary for topographic map refinement.

A more selective approach is to disrupt retinal waves by genetic deletion of the β 2-subunit of the nicotinic acetylcholine receptor (nAChR), which disrupts the second of the three stages of retinal waves. These β 2-nAChR knockout mice exhibit retinotopic map errors and diffuse terminal zones of RGC afferents in SC (McLaughlin et al., 2003b; Chandrasekaran et al., 2005; Mrsic-Flogel et al., 2005), LGN (Grubb et al., 2003; Grubb and Thompson, 2004) and V1 (Cang et al., 2005), which would cause enlarged RFs. However, this approach is not free of complications (Chalupa, 2009). Retinal waves remain in these animals, mediated by gap junctions instead of nAChRs (Sun et al., 2008), and the later glutamatergic retinal waves are not affected. Nonetheless, it is clear that these animals do not have normal spontaneous activity and that they do have retinotopic mapping errors. Thus, although activity-

dependent molecular guidance is sufficient for initial map formation, the refinement of terminal zones and retraction of miswired connections requires nAChR-mediated correlated spontaneous activity.

1.1.4.2 Sensory-evoked activity

Sensory-evoked activity is limited by the quality and accessibility of the sensory organ- vision can only occur after birth in mammals, because little light penetrates the uterus (Rao et al., 2013). In animals born with closed eyes, visually-evoked activity can occur to some extent through the closed eyelids (Shi et al., 2000; Krug et al., 2001; Townsend et al., 2003; Colonnese et al., 2010), but activity increases considerably at the time of eye opening.

Several approaches have been taken to block visually-evoked activity without affecting spontaneous activity. Binocular deprivation by eyelid suture was at first thought to have the same effect as dark rearing (DR) (Cynader et al., 1976; Leventhal and Hirsch, 1980), but was later found to cause distinct effects (Mower et al., 1981b). It was revealed that binocular deprivation does not block all light but instead blocks only patterned visual stimulation- no edges are experienced. The result of binocular deprivation is unrefined RFs in V1 and a profound reduction in visual responsiveness (Mower et al., 1981b). Binocular deprivation also causes misalignment of the eyes (Sherman, 1972), which does not occur to nearly the same extent in DR animals (White et al., 2001), and may underlie disrupted orientation tuning in these animals (Crair et al., 1998).

DR, on the other hand, blocks all visually-evoked activity and has a less profound effect than binocular deprivation on V1 physiology. DR increases the number of binocularly driven neurons and reduces their selectivity (Mower et al., 1981b). Moreover, DR animals can recover some function when given normal visual experience, whereas binocular deprivation causes permanent effects that cannot be overcome (Mower et al., 1981b).

In sum, diffuse light through closed eyelids causes more profound disruption of vision than no light at all. Thus, **patterned** visual activity is necessary to develop normal function and diffuse light-evoked activity is not sufficient (Ruthazer and Aizenman, 2010).

1.1.4.3 Instructive vs permissive activity

Spontaneous retinal waves and/or visually-evoked pattern vision could provide instructive and/or permissive activity to retinorecipient areas. Instructive processes rely on the **pattern** of activity, and thus retinal waves could underlie fine tuning of map topography. Neighboring neurons in the retina fire coincidentally during a retinal wave, which could instruct the afferents to strengthen synapses on the same or on nearby SC neurons. This could act through mechanisms of Hebbian synaptic plasticity to promote convergence onto precise axon termination zones. The fact that $\beta 2$ -nAChR knockout causes a disrupted pattern of spontaneous activity and reportedly no significant change in the overall amount of activity (Bansal et al., 2000; McLaughlin et al., 2003b; but see Chalupa, 2009), indicates that retinal waves instruct retinotopic map refinement (Chandrasekaran et al., 2005; Mrsic-Flogel et al., 2005; Xu et al., 2011).

The pattern of visually-evoked activity could also be instructive for development of RF properties. A well-studied example of a visual response property that develops through an instructive process is the tuning of V1 neurons to specific orientations of edges, usually measured electrophysiologically using bars of light (Chapman et al., 1996; Chapman et al., 1999). In a clever experiment, the optic nerves of ferrets were stimulated to fire action potentials that disrupted the normal pattern of activity after eye opening, without changing the total amount of activity (Weliky and Katz, 1997). This prevented orientation tuning from developing to the same extent as in controls. In addition, animals that experience a single orientation of lines during development exhibit more neurons that are tuned to that orientation in V1 (Hirsch and Spinelli, 1970; Hirsch and Spinelli, 1971; Sengpiel et al., 1999). Similarly, if animals are reared in an environment with a spatial grating moving in a particular direction, they develop neurons that are selective for that direction of movement in both V1 (Tretter et al., 1975; Daw and Wyatt, 1976) and SC (Flandrin and Jeannerod, 1975; Flandrin et al., 1976). Thus, for the development of orientation and direction tuning, the pattern of visually-evoked activity matters, indicating that it is an instructive process.

Permissive processes, on the other hand, do not rely on the pattern of activity but rather, the **amount** of activity. For example, activity allows calcium entry into the cell, and it is possible that the cell requires a threshold level of calcium for normal development. Perhaps the high levels of activity evoked by visual experience are essential to reach the level of calcium necessary for synaptogenesis or some other developmental property. High levels of neural activity reached through sensory experience, which cannot be provided by spontaneous activity, at least at the appropriate point in development (Crair, 1999; Huberman et al., 2008; Chalupa, 2009), also activate structural changes that prevent plasticity in mature circuits (Mataga et al., 2002; Pizzorusso et al., 2002; Mataga et al., 2004; Bence and Levelt, 2005; Pizzorusso et al., 2006; McRae et al., 2007; Balmer et al., 2009; Carulli et al., 2010). Activity-dependent neurotrophin expression could underlie the sensitivity to amounts of activity and permissive thresholds for development of RF properties.

1.1.4.4 Neurotrophins

Visually-evoked activity could be permissive for visual development via activity-dependent expression of neurotrophins. Neurotrophins activate membrane bound receptors that promote neuronal survival, function, plasticity and growth (Park and Poo, 2013). Mammals express many neurotrophins including: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4) (Huang and Reichardt, 2001). Neurotrophins bind to tropomyosin-related kinase (Trk) receptors (Bothwell, 1995). NGF binds specifically to TrkA, BDNF binds to TrkB, and NT-3 and NT-4 bind to TrkC. Activation of these receptors causes intracellular signal transduction that promotes growth. All neurotrophins also bind to the low affinity p75NTR which promotes apoptosis (Huang and Reichardt, 2001).

Visually-evoked responses are much stronger than spontaneously generated activity and cause a marked increase in the expression of many genes (Nedivi et al., 1993; Tropea et al., 2006). Activity promotes BDNF expression (Sale et al., 2004; Tognini et al., 2012) and plays a major role in the maturation of inhibitory synapses (Rutherford et al., 1997; Huang et al., 1999; Marty et al., 2000; Seil and

Drake-Baumann, 2000; Grantyn et al., 2011). Overexpression of BDNF can rescue maturation of RF properties despite DR, suggesting that a permissive level of BDNF may be required for normal visual system development (Gianfranceschi et al., 2003).

In addition, neurotrophins could play an instructive role in visual system development. For example, postsynaptic targets could release BDNF in an activity-dependent manner, requiring a specific pattern of activity. This synapse-specific BDNF release could preferentially strengthen active synapses and protect them from the pruning that occurs at inactive synapses. BDNF-TrkB signaling mediates retinocollicular arbor branching and stabilization (Marshak et al., 2007). The pattern of activity appears to interact with BDNF signaling, because blockade of pattern-detecting NMDA receptors prevents BDNF from promoting synapse elaboration (Cohen-Cory, 1999; Hu et al., 2005).

Visual experience-dependent transcription factors that regulate the expression of neurotrophins have recently been identified as having important roles in experience-dependent plasticity in V1. Npas4 is a transcription factor that is activated by visual experience and regulates BDNF and other genes that affect plasticity in V1 (Lin et al., 2008; Maya-Vetencourt et al., 2012b). Otx2 is a transcription factor that is expressed in the retina and is apparently passed trans-synaptically to V1 when a permissive level of retinal activity is reached (Sugiyama et al., 2008). There, it regulates gene expression in V1 neurons and contributes to maturation of inhibition and development of the perineuronal nets that restrict plasticity in adulthood (Beurdeley et al., 2012). Neurotrophin expression evoked by visual experience could underlie maturation of inhibition, and could prevent RF plasticity in mature circuits.

1.1.5 Role of activity in RF refinement in SC

RF refinement is an activity-dependent process, but the relative roles of spontaneously-generated and visually-evoked activity are not well understood. Neural activity is necessary for RF refinement in SC- suppression of both spontaneous and visually-evoked activity with TTX prevents refinement of RGC terminal zones (Fawcett et al., 1984; Thompson and Holt, 1989; Kobayashi et al., 1990). The pattern of neural activity is also important for RF refinement in SC. Blockade of NMDA receptor signaling during

development decreases retinotopic precision (Cline and Constantine Paton, 1989; Constantine-Paton et al., 1990; Debski et al., 1990; Simon et al., 1992) and leads to enlarged RFs in adulthood (Huang and Pallas, 2001; Razak et al., 2003). However, it is unclear whether the disruption of RF refinement is due to interruption of the pattern of stimulus-evoked activity or the pattern of spontaneous retinal activity, because these studies disrupted both.

The pattern of spontaneous activity instructs RF refinement in mouse SC, because disruption of cholinergic retinal waves in β 2-nAChR knockout mice prevents refinement of RFs (Chandrasekaran et al., 2005; Chandrasekaran et al., 2007; Wang et al., 2009). In β 2-nAChR knockout mice, RFs in LGN (Grubb et al., 2003; Grubb and Thompson, 2004) and V1 (Wang et al., 2009) do refine, in contrast to SC, indicating that mechanisms of RF refinement likely differ between visual areas. Interestingly, the β 2-nAChR knockout affects the patterning of the nasotemporal axis of SC more than the dorsoventral axis. The difference may be due to the fact that the axons are ordered along the dorsoventral axis within the optic tract before it reaches the SC, but the nasotemporal axis is mixed (Plas et al., 2005). Thus, nasotemporal axis mapping requires more organization when the optic tract reaches the SC and depends to a larger extent on patterned activity.

DR prevents visually-evoked activity, but spares spontaneous activity, and has been used to investigate the role of visually-evoked activity on RF refinement and maintenance. Spontaneous activity is sufficient for the refinement of RFs in rodent SC (Rhoades and Chalupa, 1978a; Carrasco et al., 2005; Wang et al., 2010) and zebrafish tectum (Niell and Smith, 2005). In Syrian hamsters RFs refine normally by P60 despite DR from birth (Carrasco et al., 2005).

Strobe rearing affects the pattern of visually-evoked activity but does not affect the pattern of spontaneous activity. The RF size of SC neurons is not affected by strobe rearing in Syrian hamsters (Chalupa and Rhoades, 1978b), which agrees with the above studies indicating that the pattern of visually-evoked activity does not play a major role in refinement. Taken together, these studies indicate that visual experience is not necessary for RF refinement in SC, and that the pattern of spontaneous activity instructs SC RF refinement.

1.1.6 Role of activity in development of RF properties in V1

Behavioral studies have shown that the vision of kittens is poor at the time of eye-opening (Warkentin and Smith, 1937; Mitchell et al., 1976). Thus, it was a surprise, given the unclear optical qualities of the eyes themselves (Bonds and Freeman, 1978), that V1 neurons in newborn kittens exhibited binocularity, orientation tuning, direction tuning, and in some reports, small RFs (Hubel and Wiesel, 1963; Buisseret and Imbert, 1976; Fregnac and Imbert, 1978; Braastad and Heggelund, 1985). Although some neurons appear to have mature response properties at birth, these are in the minority and are less visually responsive than adult neurons. Overlapping periods of refinement of RF properties and size occur during postnatal development (Huberman et al., 2008). The general pattern appears to be that development of RF properties is initially guided by molecular mechanisms and spontaneous activity, but fine tuning requires visual experience, as does maintenance of mature properties.

In primate V1, neurons that respond more to one eye are organized into cortical columns. The initial formation of ocular dominance columns occurs prenatally in monkeys (Rakic, 1976; Horton and Hocking, 1996) and humans (Hevner, 2000) and may depend to a large extent on molecular guidance cues (Crowley and Katz, 1999; Crowley and Katz, 2000). Spontaneous retinal activity before eye opening is also necessary for the formation of ocular dominance columns, although later visual activity shapes and maintains them (Stryker and Harris, 1986; Crair et al., 1998; Huberman et al., 2006). Orientation tuning in V1 also develops despite visual deprivation and can be observed before eye opening (Hubel and Wiesel, 1963; Hubel and Wiesel, 1974; Blakemore and Van Sluyters, 1975; Buisseret and Imbert, 1976; Fregnac and Imbert, 1978; Albus and Wolf, 1984; Chapman and Stryker, 1993; Blasdel et al., 1995; Chapman et al., 1996; Gödecke et al., 1997; Crair et al., 1998). As in the development of ocular dominance preference, visual experience is necessary for maintaining fully refined and mature, adult orientation tuning (Chapman and Stryker, 1993; Crair et al., 1998; Chapman et al., 1999; White et al., 2001). Thus, the development of ocular dominance and orientation tuning occurs early and depends to a large extent on spontaneous activity, but fine tuning and its maintenance requires visual experience.

Direction tuning seems to develop differently than ocular dominance and orientation tuning. Some V1 cells in very young kittens exhibit normal direction selectivity (Hubel and Wiesel, 1963; Pettigrew, 1974; Blakemore and Van Sluyters, 1975; Buisseret and Imbert, 1976; Fregnac and Imbert, 1978; Braastad and Heggelund, 1985), but visual experience is required for sharper selectivity in adult cats (Leventhal and Hirsch, 1980), rats (Fagiolini et al., 1994), and ferrets (Li et al., 2006). Interestingly, visual experience is not required in mice (Rocheffort et al., 2011). Maintenance of direction tuning also appears to require visual experience (Derrington, 1984).

In sum, the development of V1 RF properties requires spontaneous activity for initial development and visual experience for fine tuning and maintenance. The role of visual experience in refinement and maintenance of RF size has not been systematically studied in V1. The most relevant literature is described in the following section.

1.1.6.1 What is the role of visual experience in RF refinement and maintenance in V1?

Some researchers report that V1 RFs refine during postnatal development in rats (Fagiolini et al., 1994) and in mice (Gianfranceschi et al., 2003), as does spatial frequency selectivity in cats (Derrington and Fuchs, 1981). On the other hand, some investigators report that RFs are refined at early ages in cats (Hubel and Wiesel, 1963; Buisseret and Imbert, 1976; Fregnac and Imbert, 1978; Braastad and Heggelund, 1985), rats (Fortin et al., 1999) and rabbits (Mathers et al., 1974). In some experiments where RF sizes are assayed, only animals that were DR into adulthood were used (Ganz et al., 1968). Some experiments fail to report the age of their DR animals (Mower et al., 1981b; Fagiolini et al., 1994). Most of the experiments use different rearing conditions and techniques to measure RF size. Thus, despite the large body of previous work, conflicting results motivated us to reassess whether RFs refine without visual experience, and if they do refine, to determine whether they are maintained in a refined state without visual experience. This work is described in Chapter 2.

1.1.7 Proposed mechanisms of RF maintenance

The question of how visual experience contributes to RF maintenance relates to how plasticity is restricted in adulthood. Once neural circuits have been fine-tuned, plasticity may no longer be necessary. This developmental pattern prevents regression from the mature state, but also limits recovery from injury and disease. Understanding the mechanisms of experience-dependent prevention of plasticity will suggest novel strategies to prevent maladaptive plasticity. This work focuses on maintenance of refined RFs in SC and is described in Chapter 3.

1.1.7.1 Maintenance of inhibition maintains RFs

The role of inhibition in ocular dominance plasticity has been studied in more depth than its role in other RF properties (Hensch, 2005; Heimel et al., 2011; Levelt and Hubener, 2012; Kuhlman et al., 2013). DR reduces inhibition in V1 (Gabbott and Stewart, 1987; Bakkum et al., 1991; Benevento et al., 1992; Benevento et al., 1995; Morales et al., 2002; Chattopadhyaya et al., 2004) and delays critical period closure such that monocular deprivation can cause ocular dominance plasticity in adults long after the juvenile critical period would normally have ended (He et al., 2006). This ocular dominance shift in DR adults is blocked by exogenous enhancement of inhibition (Iwai et al., 2003; Huang et al., 2010). Reducing inhibition by genetic knockdown of GABA synthesizing enzymes GAD65 (Hensch et al., 1998) or GAD67 (Chattopadhyaya et al., 2007) delays the onset of the critical period until a threshold of GABA_Aergic inhibition is reached (Fagiolini et al., 2004). Infusion of a GAD inhibitor (Harauzov et al., 2010) or fluoxetine (Maya-Vetencourt et al., 2008), both of which reduce inhibition, reopens the critical period for ocular dominance plasticity if administered in adulthood. In sum, the strength of inhibition in V1 bidirectionally regulates the ability to induce ocular dominance plasticity.

RF plasticity in SC also depends on inhibition. DR reduces GABA immunoreactivity and GABA_AR function in SC, indicating that visual experience maintains inhibition and likely prevents RF enlargement (Carrasco et al., 2011). RF enlargement could happen through various mechanisms. The first is simply that GABA_ARs underlie lateral inhibition in SC (Binns and Salt, 1997), limiting RF size.

Loss of inhibition thus causes RFs to enlarge by weakening inhibitory surrounds. This is certainly a large part of RF enlargement in SC. Dysregulation of inhibition could also contribute to other mechanisms of RF enlargement including changes in long- or short-term synaptic plasticity described below.

1.1.7.2 Does restriction of long-term synaptic plasticity maintain RFs?

Long-term synaptic plasticity is a change in synaptic efficacy (Bliss and Lomo, 1973) that lasts at least 30 minutes and up to hours, and is an almost ubiquitous phenomenon across the brain (Malenka and Bear, 2004). Long-term plasticity is divided into two general categories: long-term potentiation (LTP)- an increase in synaptic efficacy, and long-term depression (LTD)- a decrease in synaptic efficacy. LTP occurs in V1 of young animals during RF refinement and decreases with age (Kato et al., 1991; Kirkwood et al., 1995; Maffei and Turrigiano, 2008). Extending LTP into adulthood could cause RFs to enlarge by increasing the efficacy of excitatory responses of weak synapses on the outskirts. In V1, the ability to induce LTP *in vitro* appears to follow the pattern of RF plasticity, because it is maintained by DR (Kirkwood et al., 1995; Kirkwood et al., 1996), prevented by visual experience (Kirkwood et al., 1996), and is controlled by the strength of inhibition (Wigström and Gustafsson, 1983; Artola et al., 1990). Transgenic mice that overexpress BDNF have increased inhibition, reduced LTP, and refined RFs despite DR (Huang et al., 1999; Gianfranceschi et al., 2003). This suggests that inhibition and/or LTP could underlie RF refinement in V1. On the other hand, GAD65 knockout mice have both refined RFs and normal LTP, but reduced inhibition (Hensch et al., 1998), raising the possibility that LTP correlates with refined RFs but changes in inhibition do not.

Could mechanisms of long-term plasticity underlie DR-induced RF enlargement in SC? Visual experience causes LTP at retinocollicular synapses (Zhang et al., 2000). Blocking NMDARs prevents LTP in rat SC (Zhao et al., 2006). NMDARs are necessary for refinement of retinocollicular arbors (Schmidt, 2004) and refinement of SC RFs (Razak et al., 2003). Development of inhibition in SC is accelerated by exogenous NMDAR activation, which suggests that NMDARs play a permissive role in normal developmental refinement in SC (Aamodt et al., 2000). Thus, in SC, NMDAR-dependent LTP is

likely to be necessary for RF refinement and this form of synaptic plasticity can shape RFs. However, it cannot be assumed that DR-induced RF enlargement is the reverse of refinement.

In Chapter 3, we test the hypothesis that visual experience prevents long-term plasticity from occurring, which could maintain RFs in a refined state. In this case, DR would allow long-term plasticity, which could contribute to DR-induced RF enlargement.

1.1.7.3 Does short-term synaptic plasticity maintain RFs?

The strength of synaptic transmission is dynamically affected by recent activity. A stimulation-induced change in synaptic strength that lasts from milliseconds to seconds is called short-term plasticity. In the SC, retinocollicular afferents have a high probability of neurotransmitter release that causes responses to depress with repeated stimulation, referred to as short-term depression (STD).

Sensory experience is necessary for the maturation of STD in V1 (Jiang et al., 2005; Jiang et al., 2010) and in auditory cortex (Takesian et al., 2010). The effect of experience on STD has not been investigated in SC, but could contribute to enlarged RFs after DR. For example, visual stimulation on the outskirts of a RF causes a neuron to fire a single action potential, after which the response depresses below spike threshold. This stimulus location is unlikely to be interpreted as being within the RF (by the experimenter or by the brain). If this depression is reduced, the cell will fire multiple action potentials and the location would be included in the excitatory RF center.

In Chapter 3, we test the hypothesis that STD is maintained by visual experience and that this prevents DR-induced RF plasticity. Reduced STD would increase excitability, which could cause RFs to expand.

1.2 Why study Syrian hamsters?

The Syrian hamster has been a workhorse for developmental neurobiology for decades (Schneider, 1969; Chalupa and Rhoades, 1978a; Finlay et al., 1978; Finlay and Berian, 1985). The development and experience-dependent maintenance of mammalian SC RFs was first described in Syrian

hamsters (Carrasco et al., 2005; Carrasco and Pallas, 2006). Syrian hamsters have high visual acuity relative to other rodents and rely heavily on vision for finding prey (Langley, 1985). Thus, Syrian hamsters are an advantageous species in which to study RF plasticity as a model for experience-dependent maintenance of mature function.

1.3 Clinical relevance

DR-induced RF enlargement in adulthood represents plasticity that is inappropriate and maladaptive, because it is likely to reduce visual acuity. Visual experience is necessary to prevent RF enlargement, and prevent the maladaptive plasticity (Nava and Roder, 2011) that occurs with sensory deprivation. Sensory deprivation occurs in humans with diseases of the eye such as macular degeneration and cataract (Lewis and Maurer, 2009). Studying how environmental experience prevents maladaptive plasticity could provide insight into age-related loss of sensory acuity in humans (Habak and Faubert, 2000; Leventhal et al., 2003; Betts et al., 2005).

More generally, understanding how circuits are stabilized in adulthood could contribute to the understanding of psychiatric disorders that may be caused by aberrant plasticity (Arguello and Gogos, 2012; Takesian and Hensch, 2013) including schizophrenia (Insel, 2010) and autism spectrum disorders (Rubenstein and Merzenich, 2003; Bear et al., 2004; Gogolla et al., 2009; Harlow et al., 2010).

1.4 Specific aims of dissertation

Chapter 2: SA1: What is the role of visual experience in the refinement and maintenance of RF size in SC and V1?

- SA1: Exp A: Is visual experience necessary for *refinement* of V1 RFs?
- SA1: Exp B: Is visual experience necessary for *maintenance* of V1 RFs?
- SA1: Exp C: How much visual experience is *sufficient* to prevent RF plasticity and maintain RF size in SC and V1?

Chapter 3: SA2: How does visual experience prevent RF plasticity in SC?

- SA1: Exp A: Does visual experience prevent DR-induced changes in GABA receptor function?
- SA1: Exp B: Does visual experience prevent DR-induced changes in long-term synaptic plasticity?
- SA1: Exp C: Does visual experience prevent DR-induced changes in short-term synaptic plasticity?

**2 REFINEMENT BUT NOT MAINTENENCE OF VISUAL RECEPTIVE FIELDS IS
INDEPENDENT OF VISUAL EXPERIENCE**

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2.1 Abstract

Visual deprivation is reported to prevent or delay development of mature receptive field (RF) properties in primary visual cortex (V1) in several species. In contrast, visual deprivation neither prevents nor delays refinement of RF size in the superior colliculus (SC) of Syrian hamsters, although vision is required for RF maintenance in SC. Here we report that, contrary to expectation, visual cortical RF refinement occurs normally in dark-reared animals. As in SC, a brief period of visual experience is required to maintain V1 RF refinement in adulthood. Whereas in SC, three days of visual experience within a sensitive period (P37-40) was sufficient to protect RFs from deprivation-induced enlargement in adulthood, seven days (P33-40) were required for RF size maintenance in V1. Thus, spontaneous activity is sufficient for RF refinement at these two levels of the visual pathway, and visual input is necessary only to prevent deprivation-induced RF enlargement in adulthood. These studies show that sensory experience during a late juvenile sensitive period protects the visual pathway against sensory deprivation in adulthood, and suggest that more importance may have been placed on the role of early visual experience in visual receptive field development than is warranted.

2.2 Introduction

A major question in developmental neuroscience is how early sensory experience contributes to the development of adult brain function. Experience can be in the form of light-evoked or spontaneously generated neural activity. There has been considerable debate about what the relative roles of these two types of activity are in visual system development (Ruthazer and Aizenman, 2010). Early developmental events rely on spontaneous activity before eye opening (Galli and Maffei, 1988; Wong et al., 1993; Feller et al., 1996; Weliky and Katz, 1999; Wong, 1999; Chiu and Weliky, 2001; Chandrasekaran et al., 2005; Mrsic-Flogel et al., 2005; Xu et al., 2011; Ackman et al., 2012) and in some cases light through unopened eyelids (Akerman et al., 2002; Colonnese et al., 2010). Light-evoked visual experience after eye opening plays a role in the development of some visual cortical receptive field (RF) properties but not others, for reasons that are unclear. Initial development of orientation selectivity and ocular dominance occurs without visual experience, but sharpening and maintenance of these properties requires visual experience (for review see Huberman et al., 2008; Espinosa and Stryker, 2012). In contrast, direction selectivity requires visual experience for even rudimentary development in ferrets (Li et al., 2006), but not in mice (Rocheffort et al., 2011), illustrating that species differences also exist.

RF refinement is an important aspect of the progressive improvement of visual perceptual acuity, and thus may be especially critical for survival. There is a lack of consensus regarding the time course of RF refinement and its dependence on visual experience. Part of this lack of clarity may arise from species differences and differences in the dependence of different brain regions on visual experience. In rat primary visual cortex (V1), the majority of RF refinement occurs by P30 (Fagiolini et al., 1994), whereas there is little refinement by that age in mouse V1 (Ko et al., 2013) or hamster superior colliculus (Carrasco et al., 2005) even when differences in rate of development are taken into account (Clancy et al., 2001). Synaptogenesis in V1 proceeds normally in enucleated monkeys or pre-term monkeys exposed to light, but visual experience is required for fine tuning the location of dendritic spines (Bourgeois et al., 1989; Bourgeois and Rakic, 1996), and thus is likely to be necessary for RF refinement.

The role of visual experience in development and plasticity of RFs has received little study. RF refinement is an activity-dependent process (Meyer, 1983; Thompson and Holt, 1989; Cook et al., 1999; Chandrasekaran et al., 2005; Guido, 2008; for review see Espinosa and Stryker, 2012). Previous studies have reported that RFs in primary visual cortex (V1) of dark-reared (DR) animals are enlarged (Fagiolini et al., 1994; Gianfranceschi et al., 2003) and behavioral measures show reduced visual acuity (Timney et al., 1978), but it is unclear whether the RFs never refined or whether they refined but were not maintained in a refined state.

In contrast to the critical role of vision reported for these several aspects of cortical development, early visual experience is not necessary for RF refinement in the developing visual midbrain (superior colliculus-SC) (Carrasco et al., 2005; Wang et al., 2010)(Fig. 2.1A,1-2). In hamsters DR from birth, RFs in SC refine normally by P60 (Fig. 2.1A,2) but become enlarged by P90 (Fig. 2.1A,3)(Carrasco et al., 2005). A period of light-evoked activity after, but not before, P21 is sufficient to maintain the RFs in their refined state (Fig. 2.1A,4-7), but cannot rescue RFs that have already enlarged as a result of chronic light deprivation (Carrasco and Pallas 2006) (Fig. 2.1A,8). These results from previous studies of the SC led us to challenge the notion that vision is necessary and spontaneous retinal activity is not sufficient for RF refinement in V1.

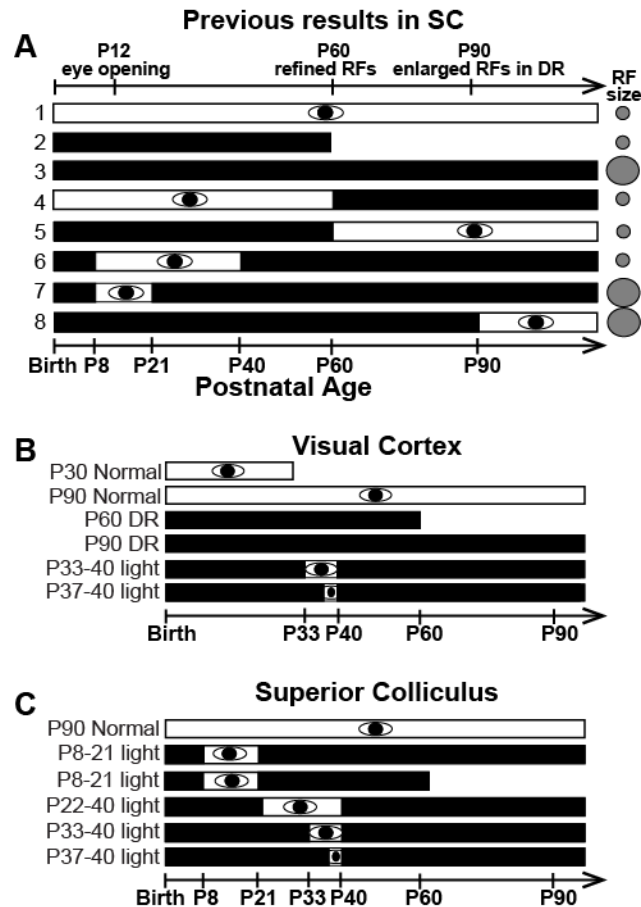


Figure 2.1. Summary of previous findings in SC

The black bars represent DR, the white bars with eye symbol represent rearing under a normal light cycle, and the gray circles represent RF size. These experiments showed that RFs in the SC refine without visual experience, but that a period of early visual experience is necessary for maintenance of the refined RFs during DR that continues into adulthood (Carrasco et al., 2005; Carrasco and Pallas, 2006). (B) Experimental design for V1 experiments. (C) Experimental design for SC experiments.

Here we report that, contrary to previous thinking, spontaneous activity appears to be sufficient for the developmental refinement of RFs in both SC and V1, although late juvenile visual experience is essential to forestall the negative effects of chronic DR that occurs in adulthood. Our findings highlight the importance of spontaneous activity and the relative unimportance of visual experience in directing

visual system development and suggest a heretofore unexamined role of visual experience in preventing future cortical plasticity.

2.3 Materials and Methods

2.3.1 *Animals and rearing conditions*

Syrian hamsters (*Mesocricetus auratus*) were used in this and the previous related studies due to their short gestation time, robust visual responses, and the abundance of data on their developmental plasticity (Razak et al., 2010). In total, 57 hamsters of both sexes were used in this study. All of the procedures involving animals met or exceeded standards of humane care developed by the National Institutes of Health and the Society for Neuroscience and were approved by the Georgia State University Institutional Animal Care and Use Committee. Hamsters were obtained from Charles River Laboratories or Harlan and bred in-house. Normally reared hamsters were kept on a 14/10 h light/dark cycle. DR hamsters were maintained in a locked, light-tight dark room protected from the hallway lights by a locked, dark anteroom with blackout curtains at each door. Animals were exposed only briefly to a dim red light for husbandry purposes, at a wavelength not visible to Syrian hamsters (Huhman et al., 1999). Pregnant dams of DR pups were moved into a darkroom before or on the day of parturition (eye opening is ~P12 in Syrian hamsters). DR hamsters that were exposed to light for 3-18 days were moved from the darkroom into a room with a 14/10 h light/dark cycle.

2.3.2 *Surgery*

Animals were prepared for terminal *in vivo* electrophysiological recordings as described previously (Pallas and Finlay, 1989; Carrasco and Pallas, 2006). Atropine (0.05 mg/kg) and dexamethasone (1 mg/kg) were administered pre-operatively, and anesthesia was induced with urethane (2 g/kg, in 4 i.p. administrations). The depth of anesthesia was monitored during the experiments by checking withdrawal reflexes, pulse and breathing rates, and blood oxygenation, with supplemental doses of urethane given as needed. For recordings made in the SC, the overlying right cortex was removed by

aspiration. Removal of the cortex has no observable effect on SC neuron RF properties in hamsters, except for a loss of direction tuning (Rhoades and Chalupa, 1978b; Razak and Pallas, 2005). The left eye was stabilized with a suture through the conjunctiva and protected with a plano contact lens.

2.3.3 Electrophysiology

Single units were recorded extracellularly with Teflon-coated tungsten electrodes (1-3 M Ω) *in vivo*. The SC recordings were made within 200 μ m of the surface to ensure that all recorded units were within the superficial, retinorecipient layers. The V1 recordings were made within the area defined as the primary visual cortex in a hamster brain atlas (Morin and Wood, 2001). Signals were amplified, filtered (10000X; 0.5 - 3 kHz; Bak Electronics A-1), and digitized using Spike2 software and CED hardware (20 kHz; Micro 1401; Cambridge Electronic Design).

2.3.4 Visual stimulus presentation

Visual stimuli used in both V1 and SC recordings were delivered to a CRT monitor positioned 40 cm from the left eye. For recordings made in V1, two different simple visual stimuli were presented: a flashing square, and a moving bar. The 2° white square on a black background was presented for 300 ms, followed by a 1 s interstimulus interval, and repeated at 2° intervals across the horizontal meridian of the screen. This stimulus was chosen because it activated the majority of units and is not susceptible to potential errors caused by activity that can continue after a moving stimulus leaves the RF. The 2° wide, 20° long, vertically-oriented, white moving bar stimulus on a black background was drifted across the screen in one and then in the opposite direction at 20 °/s, with a 3 s interstimulus interval. This stimulus was added because it is commonly used to activate V1 neurons, facilitating comparison with previous work. For recordings made in the SC, a 1° square was drifted at 14 °/s from the top to the bottom of the screen at successive nasotemporal locations, shifting 2° each presentation, as in a previous study (Carrasco et al., 2005).

2.3.5 *Analysis of RFs*

Single units were isolated by offline spike sorting using Wave_clus (Quiroga et al., 2004) and analyzed with Matlab. Analyses were conducted blind to the condition of the animal to prevent experimenter bias.

The flashing square data obtained from V1 were analyzed by plotting the location at which responses were produced as the square was progressively repositioned across the horizontal meridian of the visual field. A uniform fraction of the peak response (20%) was defined as the minimum stimulus-evoked response threshold, as in a previous study of SC (Carrasco et al., 2005). The horizontal extent of the locations within which the stimulus elicited an above threshold response was defined as the RF width. This method of RF width measurement is not affected by differences in spontaneous activity, such as may occur after DR.

The moving bar data obtained from V1 were analyzed by plotting peri-stimulus time histograms (PSTHs) with 50 ms time bins, and again using a uniform fraction of the peak response (20%) as the threshold. SC RF widths were calculated as above, using the horizontal extent of the region within which the drifting square elicited a response at least 20% of the peak response.

For the SC, in addition to the RF analysis methods outlined above, we also estimated RF areas by fitting a two-dimensional Gaussian function to reconstructions of the spatial area within which the drifting square visual stimulus elicited responses (Tavazoie and Reid, 2000; Chandrasekaran et al., 2005). Only RFs with high quality Gaussian fits were used (defined as having coefficient of determination (R^2) values ≥ 0.6). We estimated the RF area as an ellipse using the thresholds calculated as described above. To provide a measure of the shape of RFs, we used the ratio of the width of the RF to the height of the RF.

2.3.6 *Putative excitatory and inhibitory unit classification*

V1 units were classified as broad-spiking (putative excitatory) or narrow-spiking (putative inhibitory) units using two discrimination parameters calculated from the average waveform of each

extracellularly isolated unit: the ratio of the peak height to the trough depth, and the time from the peak to its return to zero voltage (Mitchell et al., 2007; Niell and Stryker, 2008; Mruczek and Sheinberg, 2012). Waveforms of each unit in V1 were averaged, interpolated, normalized and separated by *k*-means clustering (Matlab clustering toolbox). Units from recordings made with the flashing square and moving bar were analyzed separately, because in some cases the same units responded to both stimuli. Using other discrimination parameters including the slope after the peak, or the time between the trough and following peak, in place of or in addition to the return to zero time parameter, resulted in similar clusters. Some units that were used in the cluster analysis were not used for RF width analyses because they did not have a delimited RF, but they were used to estimate the number of putative inhibitory and excitatory units. RFs of putative excitatory and inhibitory V1 neurons from the groups that had enlarged RFs (P90DR and P37-40 light) were combined and compared with groups that had refined RFs (P90 Normal, P60DR, P33-40 light). RF widths were normalized to the mean of the refined RF group for each visual stimulus in order to combine both data sets. This was necessary to improve statistical power, because we expected to encounter relatively few narrow-spiking units. The majority of V1 neurons are excitatory (broad-spiking) neurons.

2.3.7 *Statistical analyses*

Student's *t*-tests or one-way analyses of variance (ANOVAs) followed by Tukey's post hoc tests were used for normally distributed data with equal variance between groups. These data are presented as mean \pm standard error of the mean (SEM). For data that did not meet these requirements, Mann-Whitney rank sum tests or Kruskal-Wallis one-way ANOVA on ranks were used, followed by Dunn's post hoc tests and presented as median \pm interquartile range (IQR).

2.4 Results

In order to investigate the role of visual experience in RF refinement, six experimental groups were used for recordings in V1 (Fig. 2.1B): normally reared P25-35 (“P30 Normal”, $n = 4$): normally reared adults >P90 (“P90 Normal”, $n = 5$), DR P55-65 (“P60DR”, $n = 8$), DR adults >P90DR (“P90DR”, $n = 5$); DR adults that received light from P33-40 (“P33-40 light”, $n = 4$), or from P37-40 (“P37-40 light”, $n = 5$). Another six groups were used for SC recordings (Fig. 2.1C): normally reared adults >P90 (“P90 Normal”, $n = 4$), adults that received light from P8-21 (“P8-21 light”, $n = 5$), P60 hamsters that received light from P8-21 and were recorded at P60 (“P8-21 light”, $n = 5$), and DR adults >P90 that had received light from P22-40 (“P22-40 light”, $n = 4$), from P33-40 (“P33-40 light”, $n = 4$), or from P37-40 (“P37-40 light”, $n = 4$).

2.4.1 Dark rearing to P60 does not prevent RF refinement in V1

Visual cortical RFs refine during development through activity-dependent mechanisms, but the roles of visual experience versus spontaneous activity are unclear. We used *in vivo* extracellular electrophysiology to test whether V1 RFs require visual experience for refinement. RF widths were measured by flashing a 2° square of light in different locations across the visual field in young (P30) and adult (P90) hamsters (Fig. 2.2A). This type of stimulus was used for determination of RF width because it effectively elicited neuronal responses but did not evoke the prolonged discharges that can occur after a moving stimulus leaves the RF (Hensch et al., 1998). We found that cortical RFs of young hamsters were markedly larger than RFs in adult hamsters (Kruskal-Wallis one-way ANOVA on ranks, $n = 182$, $p < 0.001$; Dunn’s post hoc test for P90 Normal: $14 \pm 4^\circ$, $n = 40$; vs. P30 Normal: $32 \pm 16^\circ$, $n = 37$, $p < 0.05$, Fig. 2.2B,C). This suggests that RFs refine from a very large size to a much smaller size during development, and that even 2-3 weeks after eye opening, the RFs remain approximately twice as large as in adults.

In order to determine whether visual experience is necessary for this developmental refinement of RFs in V1, we measured RFs in hamsters that were DR until P60. We chose P60 because a previous

study showed that RFs in the visual midbrain SC refine by P60 in both normally reared and DR hamsters (Carrasco et al., 2005). Large, unrefined RFs in DR animals would support the hypothesis that visual experience is necessary for refinement. Alternatively, RF refinement in V1 might occur under the influence of spontaneous retinal activity, independent of visual experience, as in the SC. In the latter case, animals that are visually deprived until adulthood should have refined, adult-size RFs. We found that the P60DR hamsters had RF widths that were not significantly different from those in the normally reared adult hamsters (P90 Normal: $14 \pm 4^\circ$, $n = 40$; vs. P60DR: $14 \pm 6^\circ$, $n = 69$, Dunn's post hoc test, $p > 0.05$, Fig. 2.2B,C). These results support the interpretation that visual activity is not necessary for developmental refinement of RFs in hamster V1.

2.4.2 *Dark rearing to P90 caused a failure to maintain RF refinement in V1*

In the SC, the RFs that have been refined during development require visual input during a late juvenile critical period in order to maintain the refined state (Carrasco et al., 2005). To determine whether this is also true in V1, hamsters were dark-reared from birth until P90, and RF widths were compared with those measured in normally-reared animals (Fig. 2.2A, P90 Normal and P90DR). Chronic DR to P90 led to significantly larger RFs than in normally reared animals (P90 Normal: $14 \pm 4^\circ$, $n = 40$; vs. P90DR: $18 \pm 6^\circ$, $n = 36$, Dunn's post hoc test, $p < 0.05$, (Fig. 2.2B,C). These data suggest that, as in the SC, visual experience is necessary to maintain the refined RFs of V1 neurons into adulthood, even though it is not necessary for the initial refinement process during postnatal development.

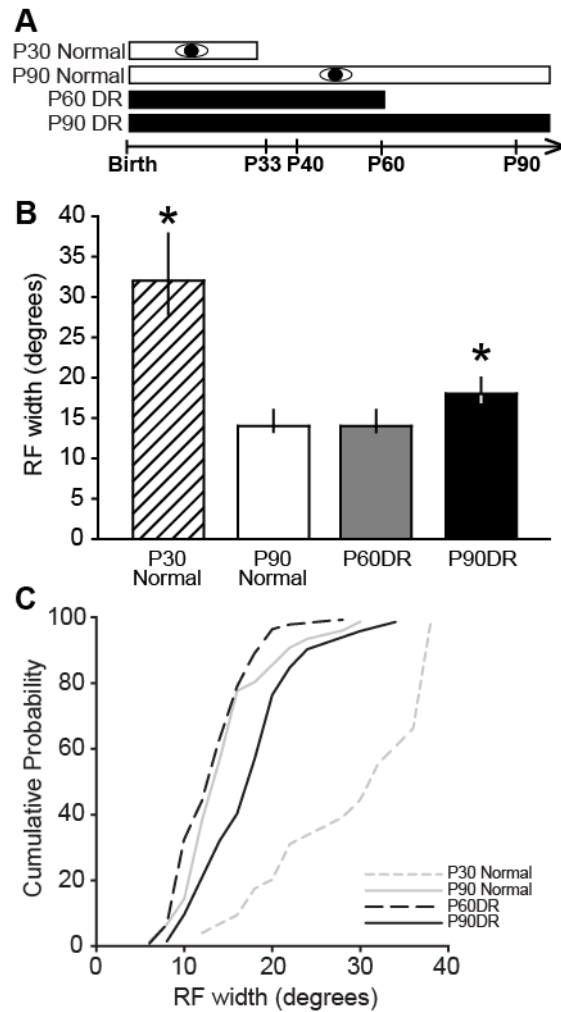


Figure 2.2. Visual experience is necessary for adult maintenance but not developmental refinement of RFs in V1.

(A) Experimental design for V1 experiments. Conventions as in Fig. 2.1. (B) To test whether visual experience is necessary for refinement and maintenance of RFs in V1, a flashing square stimulus was presented in different locations across the visual field to plot the RFs. RFs were larger at P30 than at P90 ($*P < 0.05$), showing that refinement of cortical RFs occurs in hamster cortex. DR from birth to P60 did not alter the width of RFs compared to normally reared animals, suggesting that visual experience is not necessary for refinement of visual cortical RFs during development. In contrast, DR until P90 caused an expansion of RFs ($*P < 0.05$) compared to the P90 Normal group and the P60 DR group, indicating that

DR causes enlargement of previously refined RFs. Data are presented as median \pm IQR. (C) Cumulative probability plots showing distribution of data in B.

2.4.3 One week but not 3 days of late juvenile visual experience was sufficient to maintain refined RFs in V1

After finding that visual experience is necessary for maintenance of refined RFs in V1, the duration of visual experience sufficient to maintain RFs was determined by exposing animals to 3 or 7 days of visual experience, preceded and followed by DR (Fig. 2.3A). It was previously reported that visual experience from P21-40 was sufficient to maintain RF sizes in SC despite DR (Carrasco and Pallas, 2006). We found that one week (P33-40) of late juvenile visual experience followed by DR to P90 was sufficient to maintain V1 RFs in their refined state, although 3 days from P37-40 was not sufficient (Kruskal-Wallis one-way ANOVA on ranks, $n = 112$, $p < 0.05$, P90 Normal: $14 \pm 4^\circ$, $n = 40$; P33-40 light: $16 \pm 4^\circ$, $n = 34$; P37-40 light: $16 \pm 6^\circ$, $n = 38$, Dunn's post hoc test, P90 Normal vs. P37-40 light: $p < 0.05$, Fig. 2.3B,C). Note that we report the median and IQR of these data because they are not normally distributed. Although the medians for both the P33-40 light and P37-40 light groups were 16° , there was a higher proportion of very large RFs in the P37-40 light group (see distribution in Fig. 2.3C), which accounts for the significant difference between that group and the P90 Normal group. The means and SEM of these groups are as follows: Normally reared: $14.3 \pm 0.95^\circ$; P33-40 light: $15.8 \pm 0.59^\circ$; P37-40 light: $18.2 \pm 1.18^\circ$. Thus, as in SC, late juvenile visual experience prevents DR-induced expansion of RFs in adulthood, suggesting that a similar mechanism may underlie experience-independent RF refinement and experience-dependent RF maintenance in both visual areas.

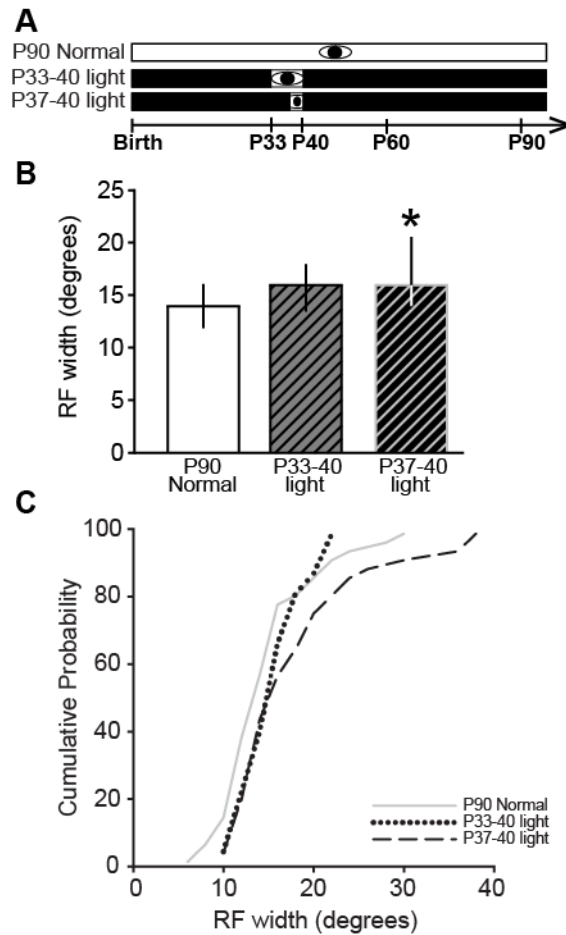


Figure 2.3. One week of late juvenile visual experience prevents deprivation induced RF enlargement in adulthood.

(A) Experimental design. Conventions as in Fig. 2.1. (B) Effect of a brief period of normal light cycle from P33-40 or P37-40 on DR-induced RF enlargement. The P33-40 light group had RFs that were normal in width. However, the P37-40 light group had significantly enlarged RFs ($*P < 0.05$, compared to P90 Normal). Data are presented as median \pm IQR. (C) Cumulative probability plots showing distribution of data in B. Note that the difference between groups is due to an increased proportion of large RFs.

2.4.4 Type of visual stimulus did not influence RF width measurements in VI

The difference in our results compared to previous reports (Fagiolini et al., 1994; Gianfranceschi et al., 2003) on the relationship between visual experience and RF development could potentially be explained by methodological differences. One difference is that we used a flashing square stimulus instead of moving bars of light as an assay for RF size. Thus, to determine whether stimulus shape and motion could influence the results, we repeated the experiments above with a moving bar stimulus. The bars were moved slowly across the visual field to reduce the prolonged discharges that can be elicited by rapidly moving stimuli. Examples of RF responses to this stimulus in Fig. 2.4 show responses from a P90 Normal unit and a P90DR unit and how PSTHs were measured to calculate RF width.

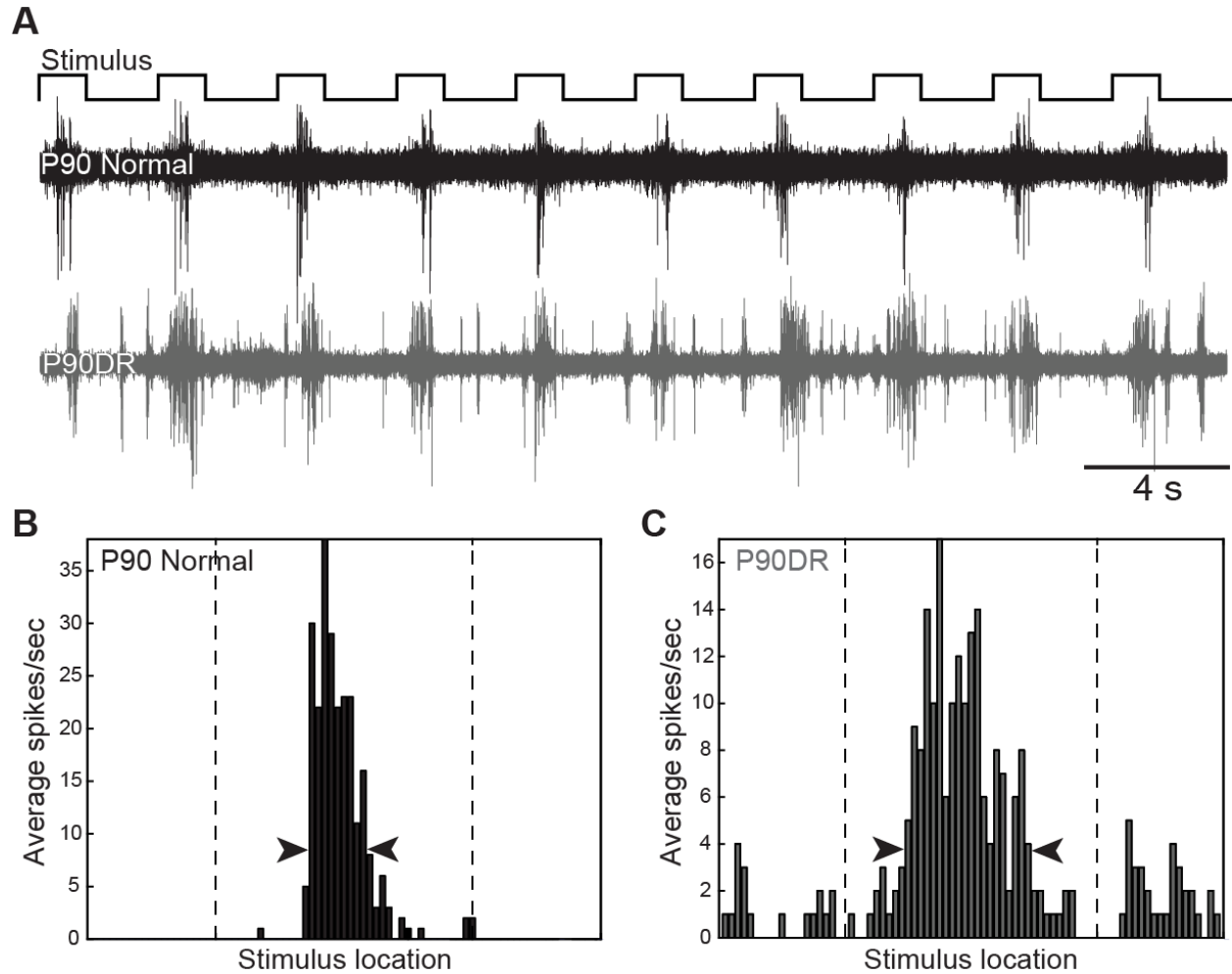


Figure 2.4. Examples of extracellular recordings and RF plots from P90 Normal and P90DR V1.

(A) Typical responses to a moving bar. The visual field area within which the neuron responds (RF width) of a neuron in the P90 Normal adult (black trace) is narrower compared to that in the neuron in the P90DR case (gray trace). RF PSTHs of the P90 Normal (B) and P90DR (C) shown in A, after single unit isolation. The dashed vertical lines represent onset and offset of the moving bar stimulus. The arrowheads indicate the 20% peak threshold used to calculate RF width.

As with the flashing square stimulus, we observed a significant effect of the duration of DR on RF width using a moving bar (Kruskal-Wallis one-way ANOVA on ranks, $n = 141$, $p < 0.001$). The RF width measured using the moving bar stimulus was similar in the P90 Normal and P60DR hamsters (P90

Normal: $10 \pm 8^\circ$, $n = 23$; P60DR: $12 \pm 8^\circ$, $n = 56$, Dunn's post hoc test, $p > 0.05$; Fig. 2.5A,B), but as expected, RFs in the P30 Normal group were significantly larger than in both the P90 normally reared group (P30 Normal: $20 \pm 13^\circ$, $n = 39$; P90 Normal: $10 \pm 8^\circ$, $n = 23$; Dunn's post hoc test, $p < 0.05$, Fig. 2.5A,B) and in the group that was DR until after P90 (P90DR: $19 \pm 13^\circ$, $n = 23$; Dunn's post hoc test, $p < 0.05$, Fig. 2.5A,B).

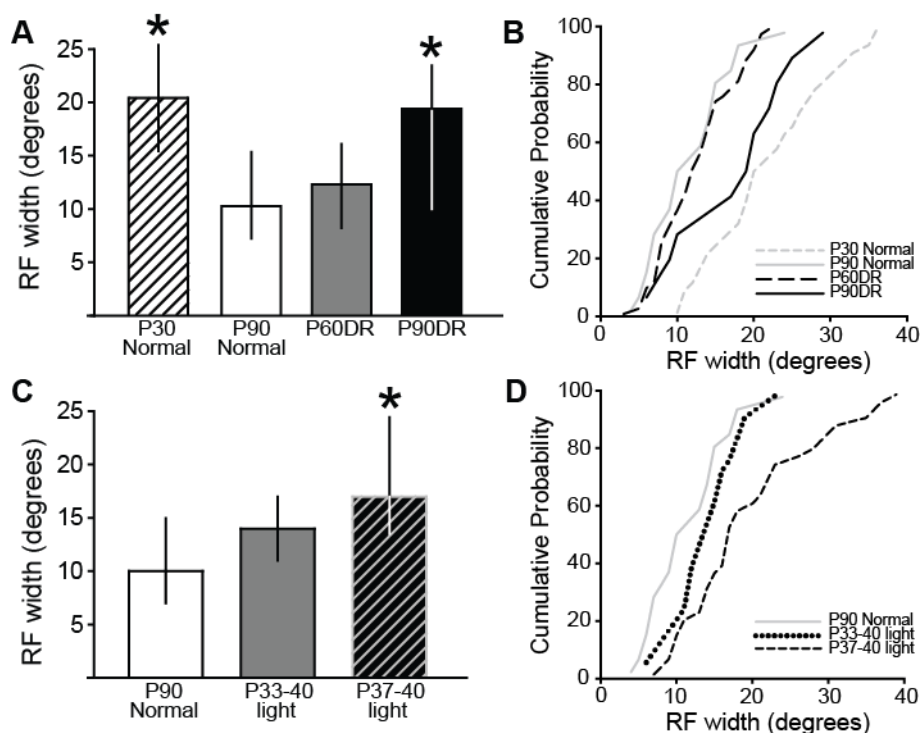


Figure 2.5. Type of visual stimulus did not influence RF width measurements in V1.

To test whether the motion or shape of the visual stimulus used to plot the RF had an effect on the RF width estimates, we repeated the experiment using a moving light bar stimulus. (A) As with the flashing square stimulus, RF width estimates using the moving bar stimulus were significantly larger in the P30 normal and P90DR groups ($*P < 0.05$) compared to the P90 Normal group. These experiments suggest that visual experience is necessary for adult maintenance but not for developmental refinement of RFs. (B) Cumulative probability plots showing distribution of data in A. (C) As with the flashing square stimulus, RF width estimates were significantly larger in the P37-40 light group. These experiments suggest that the type of visual stimulus used to estimate RF width did not affect our results, and supports

the conclusion that 7 days of visual experience beginning at P33 is sufficient to maintain V1 RFs in a refined state despite chronic DR into adulthood, but 3 days beginning at P37 is not. (D) Cumulative probability plots showing distribution of data in C. Data are presented as median \pm IQR.

We also used the moving bar stimulus to assay RF widths in adult DR animals that had experienced light from either P33-40 or from P37-40, and the results were again similar to those obtained with the flashing square stimulus. The group that experienced light for one week had RFs that were similar in width to RFs in the normally reared group, but the group that experienced light for 3 days had RFs that were significantly larger than seen in the normally reared group (P90 Normal: $10 \pm 8^\circ$, $n = 23$; P33-40 light: $14 \pm 6^\circ$, $n = 27$; P37-40 light: $17 \pm 10^\circ$, $n = 37$; Kruskal-Wallis one-way ANOVA on ranks, $n = 87$, $p < 0.001$; Dunn's post hoc tests, P90 Normal vs. P33-40 light: $p > 0.05$, P90 Normal vs. P37-40: $p < 0.05$, Fig. 2.5C,D). These results suggest that postnatal visual experience is indeed necessary for maintenance but not for refinement of RFs, and that this result is not due to the type of stimulus (flashed square or moving bar) used to measure the RFs.

To test whether RFs continue expanding after P90 in DR animals, we tested for a correlation between age and RF width within the >P90DR group. The animals in the >P90 group ranged in age from P104 to P120. RF widths measured using both stimulus types were combined because there was no significant difference in their means (Flashing square: $17.94 \pm 0.98^\circ$ vs moving bar: $17.48 \pm 1.49^\circ$, t -test, $p = 0.786$). There was no significant correlation between age and RF width ($p = 0.119$, Fig. 2.6A), suggesting that RFs do not continue to expand after P104, at least not by P120.

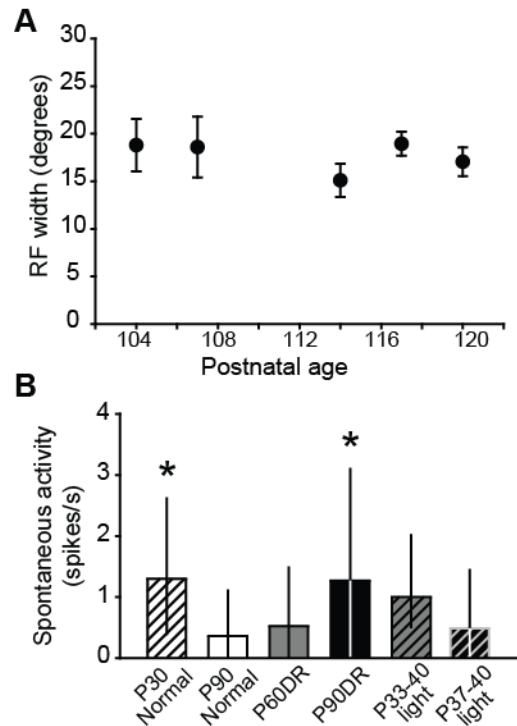


Figure 2.6. The effect of age on DR-induced RF enlargement and the effect of age and experience on spontaneous activity.

(A) There was no correlation between age after P90DR and RF width, suggesting that RFs do not continue to enlarge. Data are presented as mean \pm SEM. (B) Spontaneous activity was higher in P30 and P90DR animals compared to P90 Normal ($*P < 0.05$). Data are presented as median \pm IQR.

2.4.5 DR increased spontaneous activity in V1

Spontaneous activity was quantified for each unit as the spike rate during a 1-5 s period before the first stimulus presentation. We found that spontaneous activity was higher in the P30 Normal and P90DR groups compared to the P90 Normal group (P30 Normal: 1.29 ± 2.24 , $n = 65$; P90 Normal: 0.36 ± 1.12 , $n = 50$; P60DR: 0.52 ± 1.49 , $n = 106$; P90DR: 1.26 ± 3.10 , $n = 52$; P33-40 light: 1.00 ± 1.54 , $n = 55$; P37-40 light: 0.49 ± 1.45 , $n = 72$; Kruskal-Wallis one-way ANOVA on ranks, $n = 400$, $p < 0.001$, Fig. 2.6B). Note that our method of RF determination is independent of the level of spontaneous firing.

The finding that these groups have the largest RFs suggests a relationship between lack of refinement and levels of spontaneous activity, which could result from a loss of inhibition.

2.4.6 Both putative excitatory and putative inhibitory V1 units fail to maintain refined RFs

Inhibitory neurons provide lateral inhibition that keeps the excitatory center of RFs constrained (Sengpiel et al., 1997). The mean increase in RF size of the population of units we studied in DR animals may be caused by an increase in RFs of excitatory neurons, which constitute the majority of neurons in V1. In addition, a decrease in the RF size or strength of inhibitory neurons could contribute to the expanded RFs of the majority of neurons recorded, due to a reduction of lateral inhibition. To investigate which type of neurons exhibit enlarged RFs after DR, units were classified as being either broad-spiking or narrow-spiking (Fig. 2.7A-D). Narrow-spiking neurons are likely inhibitory neurons because their action potentials are brief compared to action potentials of excitatory neurons (McCormick et al., 1985). This difference in spike duration can be utilized to identify putative excitatory and inhibitory neurons (Mitchell et al., 2007; Niell and Stryker, 2008; Durand et al., 2012; Mruczek and Sheinberg, 2012). In this study, 17% of the units were classified as putative inhibitory neurons, which is similar to proportions reported in visual cortex of rat (15%) (Lin et al., 1986), mouse (19%) (Tamamaki et al., 2003; Niell and Stryker, 2008), cat (21%) (Gabbott and Somogyi, 1986), and monkey (20%) (Hendry et al., 1987). RFs of putative excitatory and inhibitory neurons from the groups that had enlarged RFs (P90DR and P37-40 light) were combined to improve statistical power and compared with groups that had refined RFs (P90 Normal, P60DR, P33-40 light). RFs of putative excitatory units were significantly enlarged (refined group: $100.0\% \pm 2.4\%$, $n = 162$; enlarged group: $129.5\% \pm 5.6\%$, $n = 96$, Mann-Whitney rank sum test, $p < 0.001$, Fig. 2.7E). RFs of putative inhibitory units were also significantly enlarged (refined group: $100.0\% \pm 7.9\%$, $n = 26$; enlarged group: $140.0\% \pm 12.8\%$, $n = 22$, t -test, $p = 0.008$, Fig. 2.7F). These data argue that enlargement of RFs in both excitatory and inhibitory neurons contribute to the overall enlarged RFs in groups with insufficient visual experience to maintain them in a refined state.

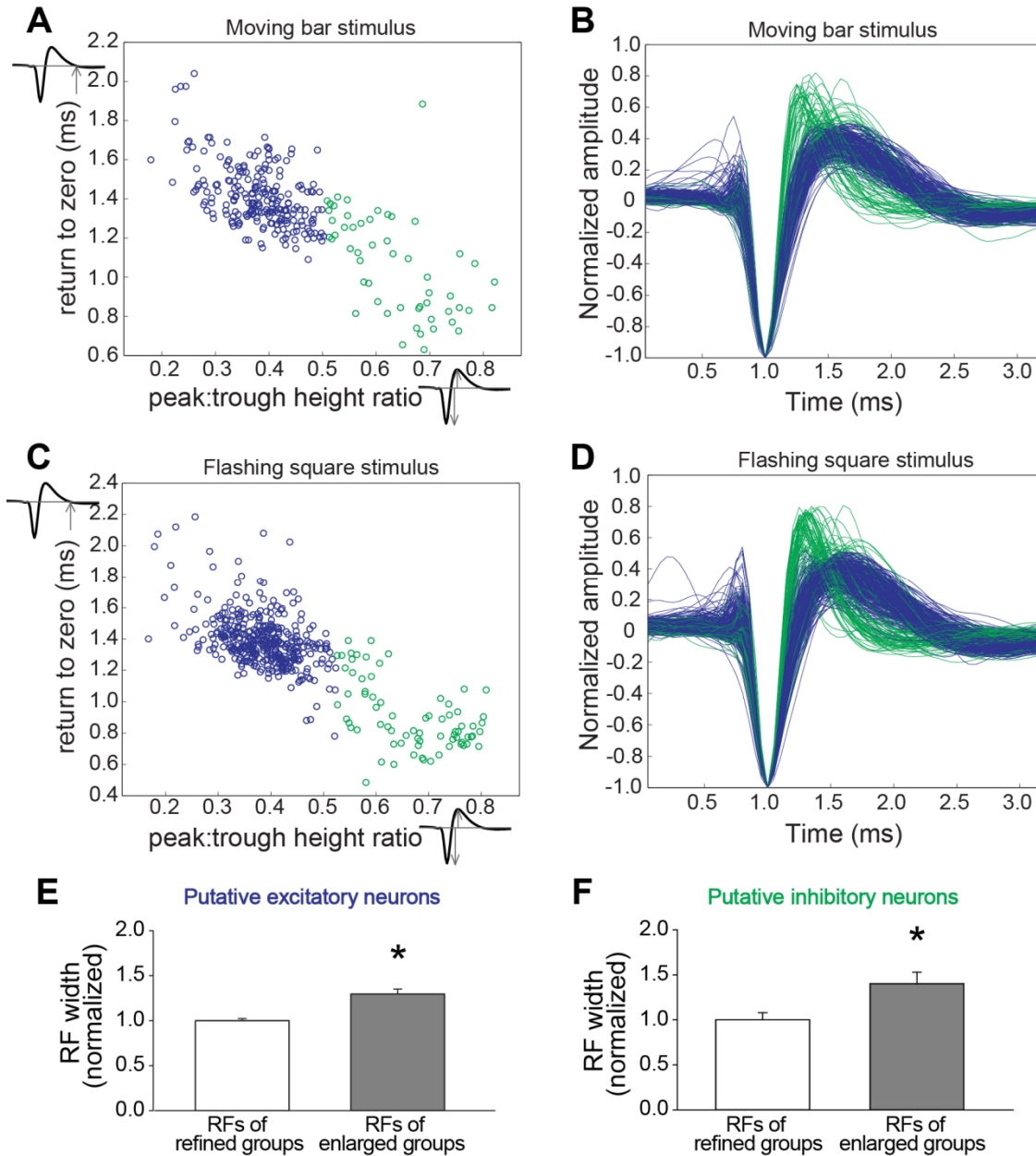


Figure 2.7. Both putative excitatory and putative inhibitory units have expanded RFs in the absence of sufficient postnatal visual experience.

Scatter plot of waveform discrimination parameters for moving bar data (A) and flashing square data (C) demonstrate categorization of broad-spiking (putative excitatory units, black) and narrow-spiking (putative inhibitory units, gray). Normalized waveforms of all units using moving bar (B) or flashing square (D) stimuli. RFs of both putative excitatory units (E) and putative inhibitory units (F) contribute

to enlarged RFs in P90DR and P37-40 light groups compared to groups with refined RFs (P90 Normal, P60DR and P33-40 light groups, $*P < 0.05$). Data are presented as mean \pm SEM.

2.4.7 Late but not early juvenile visual experience was sufficient to maintain refined RFs in SC

Given the finding that RF maintenance in V1 was achieved with 7 but not 3 days of late juvenile visual experience during visual deprivation, we investigated whether this requirement was similar in SC. The SC is essential for visual orientation in rodents (Schneider, 1969; Carman and Schneider, 1992). Both the retina and V1 send strong inputs directly to SC. In a previous study we demonstrated that visual experience from P8-40 is sufficient to maintain SC RFs, but P8-21 is not a sufficient exposure time (Carrasco and Pallas, 2006). Thus, in a related set of experiments, we tested the duration of visual experience necessary to maintain SC RF size and whether it is similar to or different from the duration of experience necessary for RF maintenance in V1. We generated four groups of hamsters that received progressively restricted durations of visual experience: 13 early days (P8-21), 18 late days (P22-40), 7 late days (P33-40) or 3 late days (P37-40), preceded and followed by DR (Fig. 2.8A). Extracellular electrophysiological recordings in superficial SC were performed to estimate RF size after P90, which is the point when RFs would have expanded in DR animals.

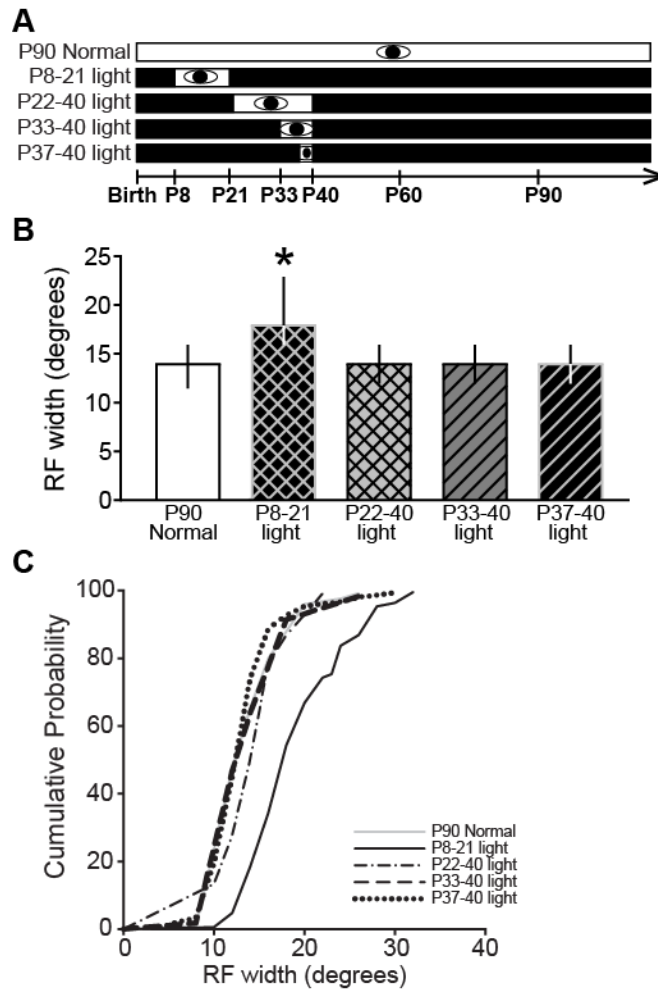


Figure 2.8. Late but not early juvenile visual experience was sufficient to maintain refined RFs in SC.

(A) Experimental design for SC study. Conventions as in Fig. 2.1. (B) Maintenance of RF width in SC during DR requires precise timing of visual experience. Animals were DR from before birth and exposed to light from P8-21, P22-40 or P33-40, followed by DR until >P90, when RFs would become enlarged during continuous DR. Late visual experience from P22-40, P33-40 or P37-40 was sufficient to maintain RF width in adulthood (>P90) but early visual experience from P8-21 was not sufficient, compared to the P90 Normal group ($*P < 0.05$). Data are presented as median \pm IQR. (C) Cumulative probability plots showing distribution of data in B.

Consistent with previous results (Carrasco and Pallas, 2006), we found an effect of the duration of visual experience on RF width in SC (Kruskal-Wallis one-way ANOVA on ranks, $n = 310$, $p < 0.001$). Early visual experience from P8-21, preceded and followed by DR, was not sufficient to maintain refined SC RF widths beyond P90 (P8-21 light: $18 \pm 6.75^\circ$, $n = 95$; vs. P90 Normal: $14 \pm 4^\circ$, $n = 62$, Dunn's post hoc test, $p < 0.05$; Fig. 2.8B,C). However, either 18 (P22-40), 7 (P33-40), or 3 (P37-40) days of late visual experience was sufficient to maintain adult size RF width beyond P90 during DR (P22-40 light: $14 \pm 4^\circ$, $n = 49$; P33-40 light: $14 \pm 4^\circ$, $n = 29$; P37-40 light: 14 ± 4 , $n = 75$, Dunn's post hoc tests, $p > 0.05$, Fig. 2.8B,C). Analysis of RF areas was consistent with analysis of RF widths (Fig. 2.9A,B). As with the width analysis, there was also an effect of visual experience on RF area (Kruskal-Wallis one-way ANOVA on ranks, $n = 275$, $p < 0.001$). Early visual experience from P8-21 was not sufficient to maintain refined RF areas beyond P90 (P8-21 light: $326 \pm 214^\circ$, $n = 79$; vs. P90 Normal: $169 \pm 140^\circ$, $n = 58$, Dunn's post hoc test, $p < 0.05$, Fig. 2.9A,B). However, the other 3 groups that received later visual experience had SC RF areas that were not significantly different from those of the normally reared animals (P22-40 light: $219 \pm 121^\circ$, $n = 45$; P33-40 light: $227 \pm 98^\circ$, $n = 22$; P37-40 light: $161 \pm 91^\circ$, $n = 71$, Dunn's post hoc test, P90 Normal vs. P22-40 light, P33-40 light, P37-40 light: $p > 0.05$, Fig. 2.9A,B).

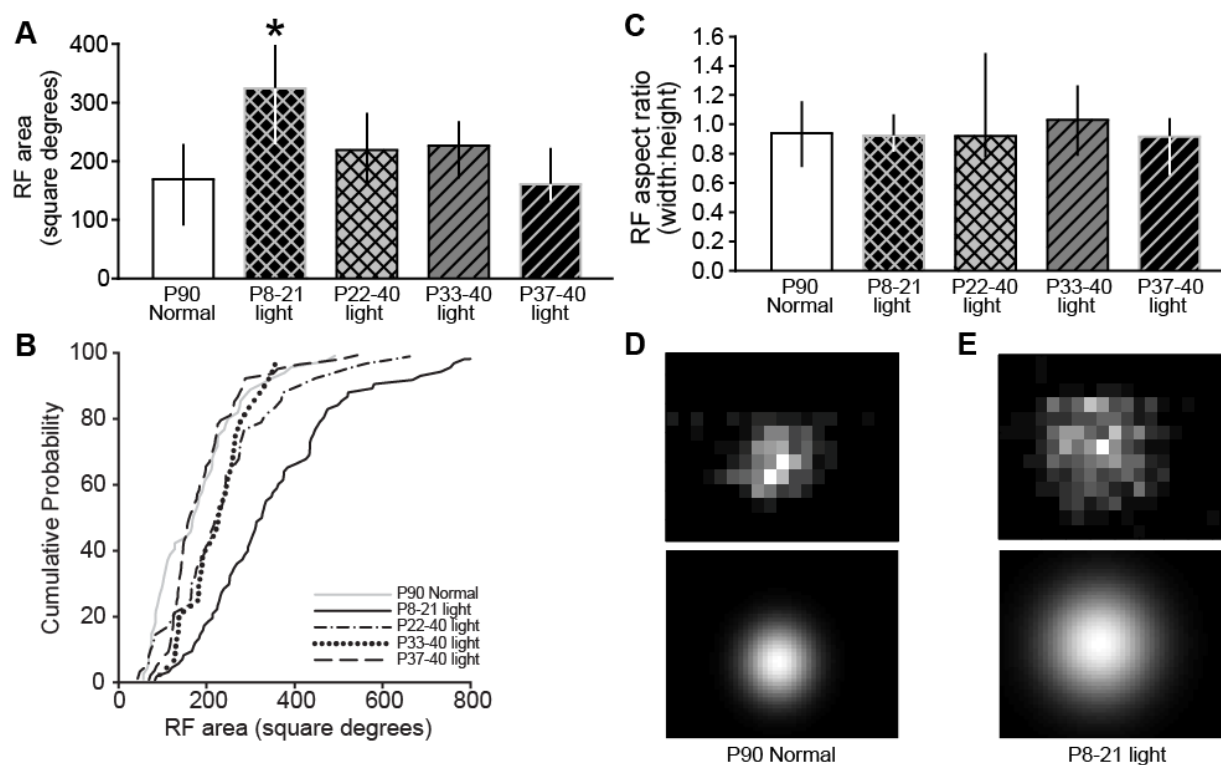


Figure 2.9. Maintenance of RF area in SC during DR requires late visual experience.

(A) Late juvenile visual experience from P22-40, P33-40 or P37-40 was sufficient to maintain RF area in adulthood (>P90) despite DR, but early visual experience from P8-21 was not sufficient, compared to the P90 Normal group ($*P < 0.05$). (B) Cumulative probability plots showing distribution of data in A. (C) The shape of RFs is maintained in groups that have expanded RFs. The width/height ratios of the RFs were not affected, even though the RF sizes were larger in the group that received light from P8-21 compared to all other groups. This suggests that RFs expanded equally in horizontal and vertical directions. (D, E) Example RF area plots: refined RF of normal adult (D, upper panel) and enlarged RF of P8-21 light (E, upper panel) and their fitted 2D Gaussians used to calculate area and width/height ratio (D and E, lower panels). Gray level represents response level, with white corresponding to peak response and black corresponding to zero. Data are presented as median \pm IQR.

A change in RF shape could indicate a rearrangement of retinocollicular inputs as seen under the condition of disrupted retinal waves (Chandrasekaran et al., 2005; Mrsic-Flogel et al., 2005). Using the

RF area estimates obtained from SC, we found that the width and height of the RFs changed in parallel, such that the enlarged RFs were expanded in both the horizontal and vertical axes (Fig. 2.9C). Although RF area was enlarged in the group that received light from P8-21, there were no differences between the width/height ratios in that or any other group (Kruskal-Wallis one-way ANOVA on ranks, $n = 275$, $p = 0.282$; P90 Normal: 0.94 ± 0.43 , $n = 58$; P8-21 light: 0.92 ± 0.25 , $n = 79$; P22-40 light: 0.92 ± 0.70 , $n = 45$; P33-40 light: 1.03 ± 0.48 , $n = 22$; P37-40 light: 0.92 ± 0.38 , $n = 71$, Fig. 2.9C). Examples of refined and expanded RFs are shown in Fig. 2.9D,E.

In sum, these data suggest that there is a sensitive period after P21 when as little as 3 days of visual experience are sufficient to prevent DR-induced RF enlargement and thus maintain a refined, adult RF size in SC.

2.4.8 Early juvenile visual experience that is not sufficient to maintain RFs does not prevent RF refinement in SC

Animals that are either normally reared or DR have refined RFs at P60 in the SC (Carrasco et al., 2005; Wang et al., 2010). Our finding that visual experience from P8-21 resulted in enlarged RFs after P90 might also be explained by a failure to maintain refined RFs, as in animals that have been DR from birth until P90. Alternatively, the enlarged RFs could be caused by RFs failing to refine. To distinguish between these hypotheses, we measured RF sizes in the P8-21 light group at P60 when normal or DR animals already have refined RFs. We found that the RFs of neurons from the P8-21 DR group were refined at P60 (P8-21 light width at P60: $12 \pm 4^\circ$, $n = 62$; vs. P90 Normal: $14 \pm 4^\circ$, $n = 62$, Dunn's post hoc test, $p > 0.05$; P8-21 light area at P60: $106 \pm 75^\circ$, $n = 66$; vs. P90 Normal: $169 \pm 140^\circ$, $n = 58$, Dunn's post hoc test, $p > 0.05$; Fig. 2.10). These results rule out the alternative hypothesis that early visual experience prevents RF refinement in SC, but is insufficient to forestall RF enlargement in adulthood.

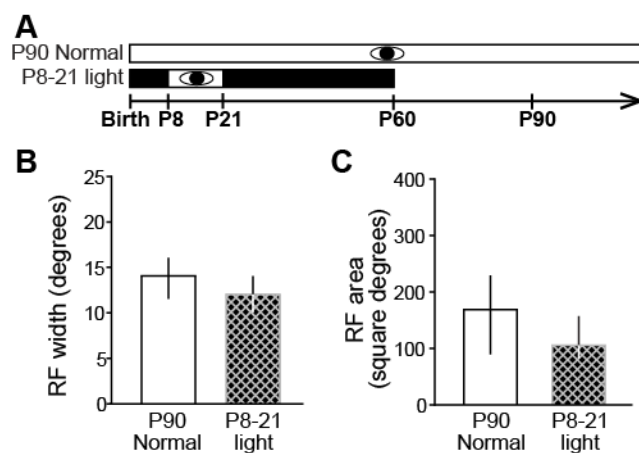


Figure 2.10. Early visual experience does not prevent refinement of RFs in SC.

This experiment tested the alternative hypothesis that enlarged RFs in animals that received early visual experience from P8-21 were caused by a failure of RFs to refine rather than a failure to maintain their refined state. Single unit RFs were measured at P60 in animals that had visual experience from P8-21 preceded and followed by DR. (A) Experimental design. Conventions as in Fig. 2.1. We found that RF width (B) and RF area (C) were not different than in P90 Normal controls, refuting the alternate hypothesis that early light exposure prevented RF refinement. Data are presented as median \pm IQR.

2.5 Discussion

The experiments described in this study demonstrate that RF refinement in V1 of Syrian hamsters occurs without visual experience, arguing that spontaneous activity is sufficient for developmental refinement of RFs in both SC and V1. One week of late juvenile visual experience from P33-40 was sufficient to prevent both SC and V1 RFs from becoming enlarged at P90, whereas 3 days from P37-40 was sufficient to protect SC but insufficient to maintain V1 RFs. These data argue that visual experience must occur during a late juvenile sensitive period in order to forestall deprivation-induced adult RF plasticity in both the form vision (retinogeniculocortical) and spatial orientation (retinocollicular) pathways, but that V1 requires a longer duration of exposure than SC (Fig. 2.11).

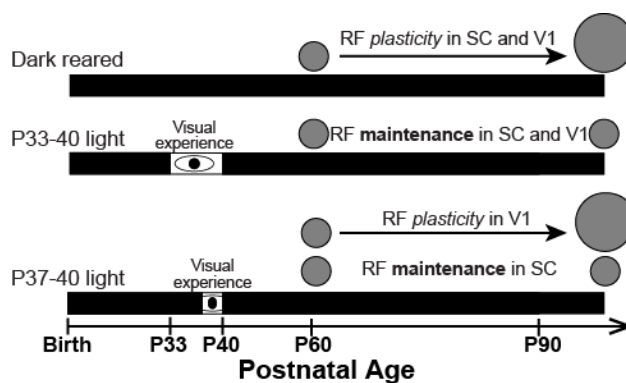


Figure 2.11. Summary of findings: Precise timing of visual experience prevents deprivation induced RF plasticity.

Our results show that DR does not prevent RF refinement, but rather causes RFs to expand after P90 in V1, as in SC. This RF plasticity can be prevented by visual experience from P33-40 in both SC and V1 and from P37-40 in SC only.

2.5.1 Spontaneous retinal activity is sufficient to refine SC and V1 RFs

The present study refutes the alternative hypothesis that the vision-independence of RF refinement in SC (Carrasco et al., 2005; Carrasco and Pallas, 2006; Wang et al., 2010) is a subcortical area-specific phenomenon. Both SC and V1 neurons can refine their RFs without visual experience, likely through spontaneous activity (Pfeiffenberger et al., 2006). This finding is consistent with reports that LGN exhibits normal physiological responses after prolonged DR (Hendrickson and Boothe, 1976; Mower et al., 1981a) and that spontaneous activity, rather than visual activity, is necessary for initial retinogeniculate refinement (Hooks and Chen, 2006). Thus, there may be a common, vision-independent mechanism for RF refinement throughout the visual pathway. Current models of visual experience-dependent refinement of RFs may need to be modified to incorporate these findings.

2.5.2 V1 requires different timing of light exposure than SC to prevent deprivation-induced plasticity

The finding that 3 days of exposure to a normal light cycle after P21 was sufficient to maintain SC but not V1 RFs during later DR is interesting because the two areas are heavily interconnected

through the cortico-collicular projection (Rhoades and Chalupa, 1978c; Pallas et al., 1988). This may indicate that visual experience stabilizes circuitry in SC earlier than in V1, or V1 may be more plastic in response to long-term visual deprivation than SC. Although it seems unlikely given that SC matures earlier than V1 (Clancy et al., 2001), we cannot rule out that 3 days of exposure may be sufficient for V1 if it occurs from P33-36, earlier than SC. Further studies are needed to explore the basis for the difference.

In the LGN, DR beginning at P20 causes weakening and an increase in number of retinal inputs to geniculate neurons; more so than DR from birth or from P15 (Hooks and Chen, 2008). This suggests that several days of visual experience are necessary for DR-induced retinogeniculate plasticity. Experiencing light from P37-40 before DR did not cause RFs to enlarge more than did DR from before birth in our study of V1. Whether earlier visual experience (P20-30) promotes RF plasticity in V1 and whether retinogeniculate plasticity underlies these potential changes is an attractive avenue for future study.

2.5.3 The shape of enlarged RFs was maintained in SC

The shape of SC RFs was not affected by DR-induced expansion of the RF areas. The initial formation of the retinocollicular map is under the control of molecular guidance cues and spontaneous activity. The anteroposterior axis is organized by graded interactions between ephrinAs and their EphA receptors (Feldheim et al., 2000) and the dorsoventral axis depends on ephrinB/EphB gradients (Hindges et al., 2002). Disruption of retinal waves during early development results in the development of elongated RFs (Chandrasekaran et al., 2005; Mrsic-Flogel et al., 2005). However, spontaneous retinal waves are not affected by DR. For this reason we did not expect to see changes in RF shape.

2.5.4 Comparison with other species

In some studies, DR has been reported to delay or prevent refinement of RFs in visual cortex of rats (Fagiolini et al., 1994) and mice (Gianfranceschi et al., 2003), and to reduce visual acuity of cats

(Timney et al., 1978) and visual responsiveness of monkeys (Regal et al., 1976). This is contrary to our results, which suggest that RF refinement is largely determined by spontaneous activity. As a burrowing rodent species, Syrian hamster pups may not experience light until later than carnivore or primate species. Indeed, Syrian hamsters develop normal circadian systems without visual experience (Kampf-Lassin et al., 2011). Alternatively, the RFs of cats, rats and mice in previous studies may have refined normally during development but enlarged by the time of recording. Some investigators reported that RFs in V1 can be normal in size at early ages in cats (Buisseret and Imbert, 1976; Fregnac and Imbert, 1978; Braastad and Heggelund, 1985), rats (Fortin et al., 1999) and rabbits (Mathers et al., 1974), (but see Fagiolini et al., 1994; Gianfranceschi et al., 2003). Thus, we argue that it is unlikely that our results are specific to hamsters.

2.5.5 The mechanism underlying RF refinement may differ from mechanisms underlying the development of other RF properties

The refinement of RF size differs in several ways from maturation of other RF properties (for review see Daw, 2006). The initial formation of ocular dominance columns in V1 occurs prenatally (Rakic, 1976; Horton and Hocking, 1996; Hevner, 2000) and despite binocular lid suture (Sherk and Stryker, 1976; Crair et al., 1998), dark rearing (Mower et al., 1981b; Stryker and Harris, 1986) or enucleation (Crowley and Katz, 1999). Orientation-specific responses and orientation maps in V1 also begin to form before eye opening (Hubel and Wiesel, 1963; Chapman and Stryker, 1993), and despite dark rearing (Singer et al., 1981) or binocular lid suture (Crair et al., 1998), but adult levels of selectivity develop over the course of several weeks and require visual experience (Bonds, 1979; Leventhal and Hirsch, 1980; Crair et al., 1998). Direction-specific responses in V1 require visual experience for normal development in ferrets (Li et al., 2006), cats (Leventhal and Hirsch, 1980) and rats (Fagiolini et al., 1994), but not mice (Rocheffort et al., 2011). Spatial frequency selectivity increases independently of visual experience up to 3 weeks postnatal in cats, but requires visual experience to improve further (Derrington and Fuchs, 1981; Derrington, 1984). Sensitivity to binocular disparity, a measure of depth perception,

increases from birth but does not develop during binocular eyelid suture in cats (Pettigrew, 1974). Our finding that RFs refine to an adult state without light-evoked activity suggests that RF refinement may involve different developmental mechanisms than some of these other receptive field properties.

2.5.6 It is unlikely that the effects of DR on SC and V1 RF size are due to changes in the retina

Dark rearing has little effect on retinal activity measured by electroretinogram (Reuter, 1976), or synaptic input to retinal ganglion cells (RGCs) and amacrine cells (He et al., 2011). Velocity tuning and direction selectivity of RGCs develops during DR (Chan and Chiao, 2008; Elstrott et al., 2008), although segregation into ON and OFF pathways is disrupted (Tian and Copenhagen, 2003). DR in turtles causes spontaneous RGC bursting, which appears to cause enlarged RFs (Sernagor and Grzywacz, 1996). In contrast, DR in rats is reported to strengthen RGC surround inhibition (Chan and Chiao, 2008) and decrease RF size of RGCs (Di Marco et al., 2009). The effects of DR on hamster retina are unknown, and we cannot rule out the possibility that changes in the retina play a part in the observed changes in SC and V1 RF size. However, it is unlikely that DR increases RGC RFs in hamsters and decreases RGC RFs in rats.

2.5.7 What mechanism underlies visual deprivation-induced enlargement of RFs?

Experience-dependent changes in inhibition are thought to be necessary for plastic changes in the visual system. Reducing inhibition in adult V1 permits ocular dominance plasticity (Maya-Vetencourt et al., 2008; Baroncelli et al., 2010; Harauzov et al., 2010; Heimel et al., 2011; Spolidoro et al., 2011; Maya-Vetencourt et al., 2012a). Because lateral inhibition defines the periphery of RFs, any change in inhibition could affect RF size directly (Ramoal et al., 1988). DR reduces inhibition in the SC, which likely underlies DR-induced RF enlargement (Carrasco et al., 2011). It is possible that in V1, as in SC, RF enlargement during DR results from loss of inhibition (Bakkum et al., 1991; Benevento et al., 1992; Benevento et al., 1995). The finding that insufficient visual experience results in enlarged RFs of putative

excitatory and inhibitory neurons suggests that lateral inhibition may be weakened in both classes of neurons.

2.5.8 What mechanism underlies visual experience-dependent prevention of RF plasticity?

Visual experience during postnatal development prevents RF expansion by forestalling RF plasticity in adulthood. Similarly, the critical period for ocular dominance plasticity is prolonged by DR, closed by visual experience (Cynader and Mitchell, 1980; Mower et al., 1983; Fagiolini et al., 1994) and increased by prior MD (Hofer et al., 2006, 2009). Because reducing inhibition in adulthood appears to reactivate cortical plasticity mechanisms (Heimel et al., 2011), visual experience-dependent strengthening of inhibition may prevent it. In V1, visual experience is necessary for developmental strengthening of inhibition (Morales et al., 2002; Katagiri et al., 2007) and for maturation of inhibitory basket cells (Sugiyama et al., 2008). The rise in inhibition initiates ocular dominance plasticity and then closes the critical period through a consolidation of inhibitory synapses (Heimel et al., 2011). Prevention of RF plasticity may also require visual experience-dependent enhancement of inhibition.

2.5.9 What is special about visual experience that spontaneous retinal activity does not provide?

Visual experience evokes higher levels of neural activity than can be provided by spontaneous activity (Crair, 1999; Huberman et al., 2008; Chalupa, 2009). Higher levels of activity may be required to increase the expression of genes critical for normal maturation (Tropea et al., 2006) and activate structural changes preventing plasticity in mature circuits (Pizzorusso et al., 2002; Bence and Levelt, 2005; Pizzorusso et al., 2006; McRae et al., 2007; Balmer et al., 2009; Carulli et al., 2010; Kind et al., 2013). Visually-driven activity increases Npas4, a transcription factor that upregulates plasticity-related genes in V1 such as brain-derived neurotrophic factor (BDNF) (Lin et al., 2008; Maya-Vetencourt et al., 2012b), which in turn stimulates maturation of inhibitory synapses (Rutherford et al., 1997; Huang et al., 1999) and the development and maintenance of visual acuity (Gianfranceschi et al., 2003; Heimel et al., 2010; Schwartz et al., 2011).

2.5.10 Maladaptive plasticity and age-related loss of acuity in humans

Sensory deprivation occurs in humans with diseases of the eye such as macular degeneration and cataract (Lewis and Maurer, 2009), and as in our model, RF expansion and a loss of visual acuity may result. A common mechanism for both RF expansion and loss of sensory acuity may be inhibitory plasticity; reduction of inhibition could enhance the gain of sensory signals, but this comes at the expense of discriminative ability. Indeed, our result that DR until >P90 increased spontaneous activity could be the result of reduced inhibition. Studying how sensory experience prevents maladaptive plasticity could provide insight into age-related loss of sensory acuity in humans (Habak and Faubert, 2000; Leventhal et al., 2003; Betts et al., 2005). Moreover, sensory circuits may develop to a greater extent under conditions of sensory deprivation than previously appreciated. A focus on blocking plasticity and thus maintaining existing sensory processing capacity, rather than enhancing plasticity, may be a beneficial and safer route to recovery from these disorders. Future work investigating how visual experience forestalls maladaptive plasticity will contribute to our understanding of sensitive periods and how they are regulated.

2.6 Acknowledgements

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3 VISUAL EXPERIENCE PREVENTS METAPLASTICITY OF GABA_B RECEPTOR-DEPENDENT SHORT-TERM DEPRESSION IN ADULT SUPERIOR COLLICULUS

Timothy S. Balmer and Sarah L. Pallas

3.1 Abstract

Regulation of critical period plasticity prevents regression of mature circuits to an immature state.

Development of GABAergic inhibition is essential for regulation of plasticity. In the superior colliculus (SC), brief, early visual experience preserves refined receptive fields (RFs) into adulthood in dark reared (DR) animals by stabilizing GABAergic inhibition, through an unknown mechanism. Using an acute slice preparation we tested whether early visual experience protects adult SC from subsequent deprivation-induced RF enlargement through alterations in synaptic plasticity. Long-term plasticity was not affected by visual deprivation, indicating that it does not underlie deprivation-induced RF enlargement. In contrast, short-term plasticity was affected by visual deprivation. GABA_BR-mediated paired pulse depression was increased in slices from DR animals. This increase was mimicked by GABA_AR blockade in slices from normally reared animals, suggesting that experience-dependent maintenance of GABA_AR function prevents a change in probability of neurotransmitter release. GABA_BR-mediated short-term depression (STD) in response to high frequency stimulation (such as occurs during vision) was reduced in slices from DR animals. This change was mimicked in slices from normal animals by reducing GABA release. Thus, early visual experience-dependent maintenance of GABAergic inhibition prevented later deprivation-induced dysregulation of STD. A difference of Gaussians RF model showed that STD could affect RF size during the first moments of visual stimulation, and that reduced STD elicited by high frequency stimulation may contribute to enlarged RFs in the SC of DR animals. Identifying how plasticity is restricted in mature circuits could instruct therapies to enhance recovery of function in adults.

3.2 Introduction

Development of sensory pathways requires robust plasticity during critical periods, but when neural circuits have matured this plasticity is no longer necessary and is restricted. This restriction stabilizes circuits and prevents regression from the mature state, but also limits recovery from injury and disease. The mechanisms that underlie the transition from flexible to stable circuits remain unclear, yet it is of great importance to elucidate how plasticity is regulated across life stages.

Visual receptive field (RF) refinement occurs during development, increasing perceptual acuity. It occurs in the absence of visual experience in both the superior colliculus (SC) (Carrasco et al., 2005; Wang et al., 2010) and primary visual cortex (V1) (Balmer and Pallas, 2013; Sarnaik et al., 2013). Thus, spontaneous activity alone is sufficient to refine RFs. Late juvenile visual experience is necessary to maintain the refined RFs into adulthood, however (Carrasco and Pallas, 2006; Balmer and Pallas, 2013). DR-induced RF enlargement in SC occurs in part through reduced inhibition (Carrasco et al., 2011). Although it is clear that sensory deprivation reduces inhibition (Benevento et al., 1995; Micheva and Beaulieu, 1995; Kotak et al., 2008) and promotes plasticity (Hensch et al., 1998), the underlying mechanisms are not understood. Here, we investigate the synaptic mechanism through which visual experience stabilizes inhibition and thus restricts SC neuron plasticity in adulthood. We test the hypothesis that dysregulation of inhibition in DR SC results in altered long- or short-term synaptic plasticity that contributes to chronic enlargement of RFs following deprivation. Thus, we hypothesize that visual experience causes metaplasticity in SC. Metaplasticity occurs when a priming event affects later plasticity. In the present study, visual experience is a priming event that restricts later plasticity caused by visual deprivation. Reducing inhibition can cause metaplasticity by increasing the ability to induce long-term synaptic plasticity (Artola et al., 1990), which could strengthen synapses along the outskirts of the RF, increasing RF size. For example, in V1, DR reduces inhibition (Morales et al., 2002) and prolongs the age at which long-term plasticity can be induced (Kirkwood et al., 1995). In addition, dysregulation of inhibition may cause altered presynaptic inhibition and/or neurotransmitter release

probability that could affect short-term synaptic plasticity and could contribute to disrupted sensory processing and enlarged RFs. The effects of visual experience on long- and short-term plasticity in SC are unclear. It would be of interest to know whether the effects of deprivation are similar in different sites within the visual pathway, and if so, whether they share a common or distinct mechanism.

We present evidence here that early visual experience prevents RF plasticity in adult SC by stabilizing GABAergic inhibition and thus maintaining GABA-mediated short-term depression of excitatory synapses. We found that the reductions in GABA_AR-mediated inhibition and GABA content in DR SC shown in a previous study (Carrasco et al., 2011) cause dysregulation of GABA_BR-mediated inhibition, which disrupts short-term (but not long-term) plasticity. Deprivation-induced metaplasticity of STD contributes to RF plasticity in adulthood, which is normally restricted by experience-dependent maintenance of inhibition and STD.

3.3 Materials and Methods

3.3.1 *Animals and rearing conditions*

Syrian hamsters (*Mesocricetus auratus*) of both sexes were used in this and the previous related studies due to their short gestation time, robust visual responses, and the abundance of data on their developmental plasticity (Chalupa and Rhoades, 1977; Razak et al., 2010). All of the procedures involving animals met or exceeded standards of humane care developed by the National Institutes of Health and the Society for Neuroscience and were approved by the Georgia State University Institutional Animal Care and Use Committee. Hamsters were obtained from Charles River Laboratories or Harlan and bred in-house. Normally reared hamsters were kept on a 14 /10 h light/dark cycle. DR hamsters were maintained in a light-tight dark room and exposed only briefly to a dim red light for husbandry purposes, at a wavelength not visible to Syrian hamsters (Huhman et al., 1999). Pregnant dams of DR pups were moved into the darkroom prior to parturition.

3.3.2 *Slice preparation*

Hamsters were deeply anesthetized with isoflurane and the brain was rapidly extracted into ice-cold 95% O₂/5% CO₂ saturated artificial cerebral spinal fluid containing kynurenic acid (KA-ACSF) (in mM): 123 NaCl, 2.5 KCl, 1 NaH₂PO₄, 1.3 MgSO₄, 26.2, NaHCO₃, 11 glucose, and 2.5 CaCl₂, 0.8 thiourea, 2 sodium pyruvate, 0.4 ascorbic acid, and 1.2 kynurenic acid. The glutamatergic antagonist kynurenic acid was included in the KA-ACSF to suppress any excitotoxic effects of glutamate release that may occur due to tissue slicing. Parasagittal (SC) or coronal (V1) slices were cut at 350 μm using a vibratome and incubated in oxygenated, 32°C KA-ACSF for 1 h followed by the same solution with kynurenic acid omitted for >1 h at room temperature. For recording, individual slices were transferred to a submerged type recording chamber and superfused with the above solution heated to 28°C, minus the kynurenic acid, thiourea, sodium pyruvate and ascorbic acid, at a rate of 1-2 ml/min. In some long-term plasticity experiments the bath temperature was raised to 32°C or 35°C, but the results were not different from the 28°C temperature results and thus the data were combined.

3.3.3 *Recording procedures*

Recording pipettes were pulled from borosilicate glass (1.5/0.86 mm OD/ID, Narashige PP-830) to resistances from 2-6 MΩ when filled with ACSF. Signals were amplified and low-pass filtered (2-3 kHz, Multiclamp 700B) and digitized using Signal software and CED hardware (50 kHz, Micro 1401; Cambridge Electronic Design).

3.3.4 *Analysis of long-term plasticity*

To evoke field potential responses, electrical stimuli with 50-100 μs pulse durations were delivered to the stratum opticum of the SC through a concentric bipolar stimulating electrode (Platinum/iridium, FHC Inc., Cat. No. CBBPC75). Stimulation intensity was adjusted to 50-75% of the maximum evoked response. Test stimuli were delivered at 20s intervals over at least 10 minutes of stable recording before and 45 min after the inducing stimulation. Induction protocols that have been shown to

produce long-term plasticity in SC in other rodents were used, including 50Hz 20s, 20Hz 20s and 1Hz 300s (Okada and Miyamoto, 1989; Lo and Mize, 2002; Zhao et al., 2006). To determine whether there was a long-term change in synaptic strength after application of the inducing stimulus, the mean peak response during baseline recordings was compared to the mean peak response during an interval 30-40 min after induction. The example field excitatory postsynaptic potentials (fEPSPs) shown are averages of 5-10 trials.

To induce LTP in V1, the stimulation electrode was placed between the white matter and layer 6 and the recording electrode was placed in layer 2/3. Theta burst stimulation (TBS) consisted of 3 episodes delivered at 10 s intervals consisting of 10 trains delivered at 5 Hz each consisting of 4 pulses at 100 Hz as described previously (Kirkwood et al., 1995).

3.3.5 PPR analysis

Paired pulse ratio (PPR) was calculated as the mean of the second response divided by the mean of the first response over a series of trials (Kim and Alger, 2001). In experiments in which the signal did not return to zero before the second pulse, the amplitude of the second pulse was measured relative to the signal during 1 ms before the stimulus artifact. When multiple inter-pulse intervals were used, the stimulus intensity was set to 25% of the maximum. In order to reduce the likelihood of a ceiling effect caused by complete depression of the second pulse (PP2), we increased the stimulus intensity to 75% of the maximum in experiments in which pharmacological agents were applied. Under these conditions, we did not always observe higher paired pulse depression (PPD) in slices from DR animals, which was not unexpected (Platt and Withington, 1997; Kim and Alger, 2001).

3.3.6 Recovery from STD analysis

A conditioning stimulus train consisting of ten 100 μ s pulses was delivered at 100 Hz in order to cause strong STD. Stimulation intensity was set to 75% of maximal. A test pulse was delivered 100, 200, 400, 800 or 1200 ms after the conditioning train to measure recovery from STD. Trials were repeated at 1

min intervals. Test stimuli were normalized relative to the first conditioning pulse under the same bath conditions. The time constant of recovery from STD was calculated as the time to reach $1 - e^{-1} = 63.2\%$ recovery from an exponential that was fit to the relative fEPSP amplitudes from 100 - 1200 ms. In experiments in which a drug was bath applied, stimuli were paused for 5 - 20 min for the drug to take maximal effect.

3.3.7 Statistical analysis

Student's t-tests or one-way or two-way analyses of variance (ANOVA), followed by Tukey's post hoc tests were used for normally distributed data with equal variance between groups. For data that did not meet these requirements, Mann-Whitney rank sum tests were used. 'n' values refer to the number of slices. Data are presented as mean \pm standard error of the mean.

3.4 Results

The retinocollicular midbrain visual circuit is important for spatial orientation to visual objects (Schneider, 1969). Visual experience is necessary to maintain refined RFs and high visual acuity (Carrasco et al., 2005; Balmer and Pallas, 2013), but it is unclear what mechanisms underlie visual experience-dependent restriction of RF plasticity in the retinocollicular circuit. Here we examine the role of visual experience in metaplasticity of long- and short-term changes in synaptic strength in acute brain slices from Syrian hamsters that were either normally reared or DR from birth until adulthood (P60-70 or >P90).

3.4.1 Characteristics of excitatory postsynaptic field potentials (fEPSPs) recorded from the superficial gray layer of the SC

In order to test the role of visual experience in mechanisms of synaptic plasticity, we utilized an acute SC slice preparation. Retinocollicular afferents are easily visualized entering the rostral SC below the superficial gray layer in parasagittal brain slices. The majority of the axons in the optic layer are RGC

axons, although some are visual cortical projections (Rhoades et al., 1991). Both projections are almost entirely glutamatergic (Lund and Lund, 1971; Mize and Butler, 1996), although a small number of GABAergic RGCs have been reported (Caruso et al., 1989; da Costa et al., 1997).

Figure 3.1 shows how the extracellular field excitatory postsynaptic potential (fEPSP) was characterized for subsequent measurements. Stimulating the glutamatergic afferents in the optic layer (stratum opticum) caused a fEPSP in the superficial gray layer. These fEPSPs are excitatory postsynaptic signals, because they were blocked by bath-applied ionotropic glutamate receptor antagonists CNQX (1 μ M) and APV (100 μ M) (Fig. 3.1A), depressed during high frequency stimulation (Fig. 3.1B), and decreased in latency with increased stimulation intensity (Fig. 3.1C). The fEPSP is likely caused by a combination of synaptic and somatic current sources, because single-unit spikes were occasionally observed near its peak (Fig. 3.1D). The short latency (\sim 3 ms) and short duration (\sim 5 ms) of the fEPSP is consistent with a monosynaptic response, although we do not rule out the possibility of polysynaptic components. Note that though the fEPSP is a postsynaptic response caused by glutamate release, both excitatory and inhibitory postsynaptic neurons are innervated by retinocollicular afferents (Mize, 1988, 1992).

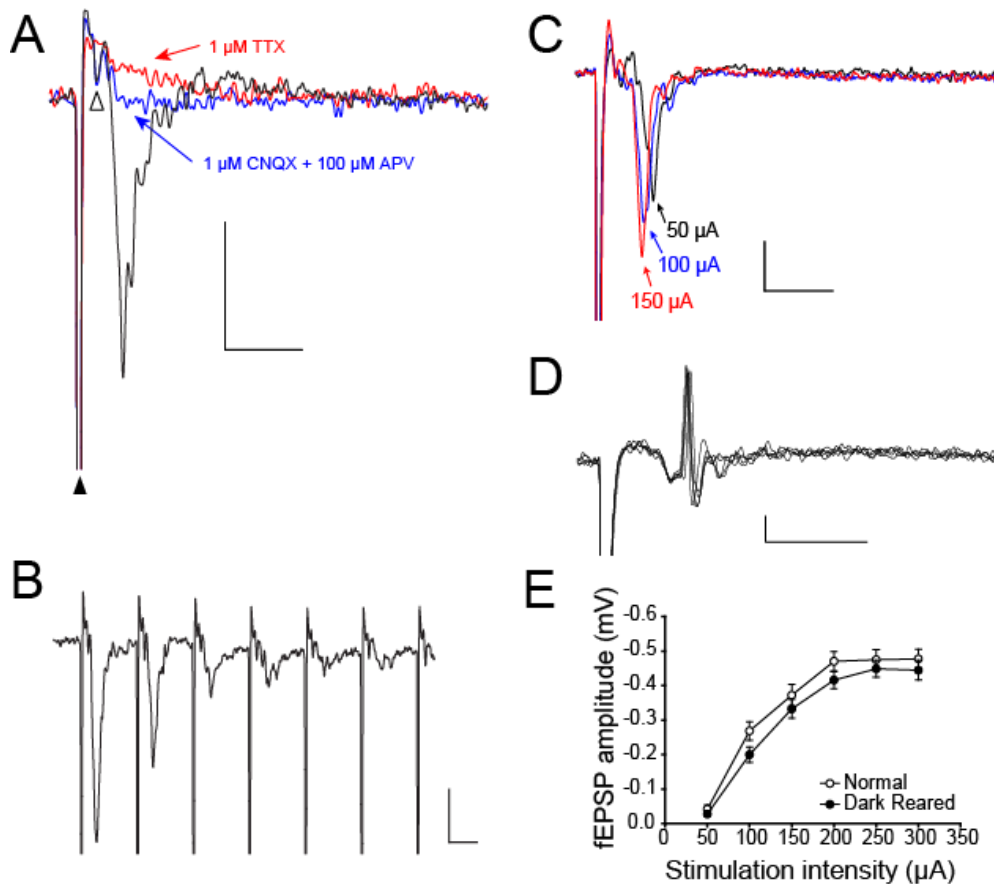


Figure 3.1. The evoked field potential in SC is an excitatory postsynaptic potential (fEPSP)

A) The postsynaptic signal is excitatory, because blocking AMPA and NMDA-type glutamate receptors with CNQX and APV completely blocked the field potential (blue trace; stimulus artifact marked with black triangle). Under glutamate receptor blockade a small presynaptic potential remained (open triangle), which was blocked by tetrodotoxin (TTX) (red trace). B) Decreased responses during rapid (100Hz) stimulation suggests a postsynaptic signal. C) Monotonically decreasing latency at increasing stimulation intensities also suggests a postsynaptic signal. D) Action potentials are occasionally observed that coincide with the peak of the fEPSP, indicating that it is likely a combination of current sources including postsynaptic dendrites and somata. Several overlain traces show that the spike occurs at a consistent latency. Reducing stimulus intensity caused the spike to disappear. E) Current evoked fEPSP responses were not significantly affected by visual experience. Scale bars in A-D 0.2 mV, 5 ms.

Reduced inhibition in DR SC (Carrasco et al., 2011) could cause increased excitability that could contribute to enlarged RFs. We measured the amplitude of fEPSPs elicited by stimulating the optic layer with increasing stimulus intensity. The fEPSP amplitude was not different between rearing conditions at any stimulus intensity, supporting the prediction that DR does not affect current-evoked excitability in SC (Two-way repeated measures ANOVA, $F(1, 233) = 1.985$, $N = 40$, $P = 0.167$, Fig. 3.1E). This result was not unexpected, given the preponderance of homeostatic regulatory mechanisms in the central nervous system that may prevent reduced inhibition from increasing overall excitability (Turrigiano, 2011; Wenner, 2011; Maffei et al., 2012) and the lack of increased excitability in DR SC *in vivo* (Carrasco et al., 2005).

3.4.2 Long-term plasticity in SC is not affected by visual experience

In V1, long-term plasticity is maximal during the critical period for ocular dominance plasticity and declines thereafter, but is maintained at the maximal level in V1 of DR animals (Kirkwood et al., 1995). In this series of experiments we tested whether long-term plasticity varies in strength during the critical period for RF plasticity in the SC. SC RFs are large at birth and undergo a period of refinement between birth and P60 (Carrasco et al., 2005). DR animals follow the same pattern of refinement, but between P60 and P70 the RFs enlarge. 3 days of light at P37-40 prevents enlargement in adulthood after P60 (Balmer and Pallas, 2013). It is possible that long-term potentiation (LTP) could have led to RF enlargement between P60 and P70. For example, weak excitatory synaptic inputs on the outskirts of a DR cell's RF could be potentiated that would normally have remained weak with normal visual experience. We predicted that SC slices from DR but not normally reared animals could exhibit juvenile levels of long-term plasticity between P60 and P70.

As expected, long-term plasticity could not be induced in slices from normally reared adults (P60-70). However, the stimulation paradigm also failed to induce long-term plasticity in slices from age-matched DR animals. The summary of experiments using a 50Hz 20s induction protocol is shown in (Fig. 3.2A). 1Hz 300s and 20Hz 20s induction protocols were also used, with similar results. Although

afferent stimulation such as this is unlikely to occur *in vivo*, these protocols have been used to induce long-term plasticity in SC *in vitro* (Okada and Miyamoto, 1989; Lo and Mize, 2002; Zhao et al., 2006). The mean fEPSP amplitude from 30-40 min post induction relative to the mean fEPSP amplitude during the 10 min baseline was not significantly different between rearing conditions for any induction protocol (Student's t-tests: 1Hz 300s Normal: 0.970 ± 0.0739 , $n = 5$ vs. DR: 0.947 ± 0.0288 , $n = 6$, $P = 0.758$ 20Hz 20s Normal: 0.975 ± 0.0307 , $n = 14$ vs. DR: 1.029 ± 0.0399 , $n = 11$, $P = 0.282$; 50Hz 20s Normal: 0.975 ± 0.0287 , $n = 8$ vs. DR: 0.987 ± 0.0415 , $n = 7$, $P = 0.826$, Fig. 3.2B). It is therefore unlikely that RF enlargement in DR animals is the result of maintained or reactivated long-term plasticity.

Because the largest differences in synaptic plasticity may be in the age group with the largest differences in RF size, we also investigated long-term plasticity in >P90 animals that had either unrefined (DR) or refined (Normal) RFs. By P90 the RFs of DR animals have reached their maximum size (Carrasco et al., 2005). We found no significant differences in mean levels of long-term plasticity between slices from >P90 normal and DR adults. The mean fEPSP amplitude from 30-40 min post induction stimuli relative to the mean fEPSP amplitude during the 10 min baseline was not significantly different between rearing conditions (Student's t-tests: 1Hz 300s Normal: 1.036 ± 0.0507 , $n = 10$ vs. DR: 0.989 ± 0.0344 , $n = 8$, $P = 0.489$ 20Hz 20s Normal: 0.927 ± 0.0417 , $n = 7$ vs. DR: 0.899 ± 0.0617 , $n = 8$, $P = 0.726$; 50Hz 20s Normal: 1.037 ± 0.0445 , $n = 8$ vs. DR: 1.032 ± 0.0189 , $n = 7$, $P = 0.920$, Fig. 3.2C-D). These results suggest that the ability to elicit long-term plasticity does not correlate with the timing of changes in RF size, and that neither enlargement of RFs, nor the maintenance of enlarged RFs during DR requires long-term plasticity.

As a positive control to show that the brain slices were indeed healthy enough to induce long-term plasticity, we tested the ability to induce LTP at a synapse known to produce it reliably- the white matter (WM) to layer 2/3 synapse in V1. As previously shown in rats (Kirkwood et al., 1995), theta burst stimulation (TBS, see methods) caused a significant potentiation of the fEPSP in slices from DR but not normally reared animals (Normal: 1.025 ± 0.0337 , $n = 8$ vs. DR: 1.214 ± 0.0550 , $n = 7$, Student's t-test, P

< 0.05, Fig. 3.2E-F). Thus, we argue that the inability to induce long-term plasticity in SC was not an artifact of slice preparation methods.

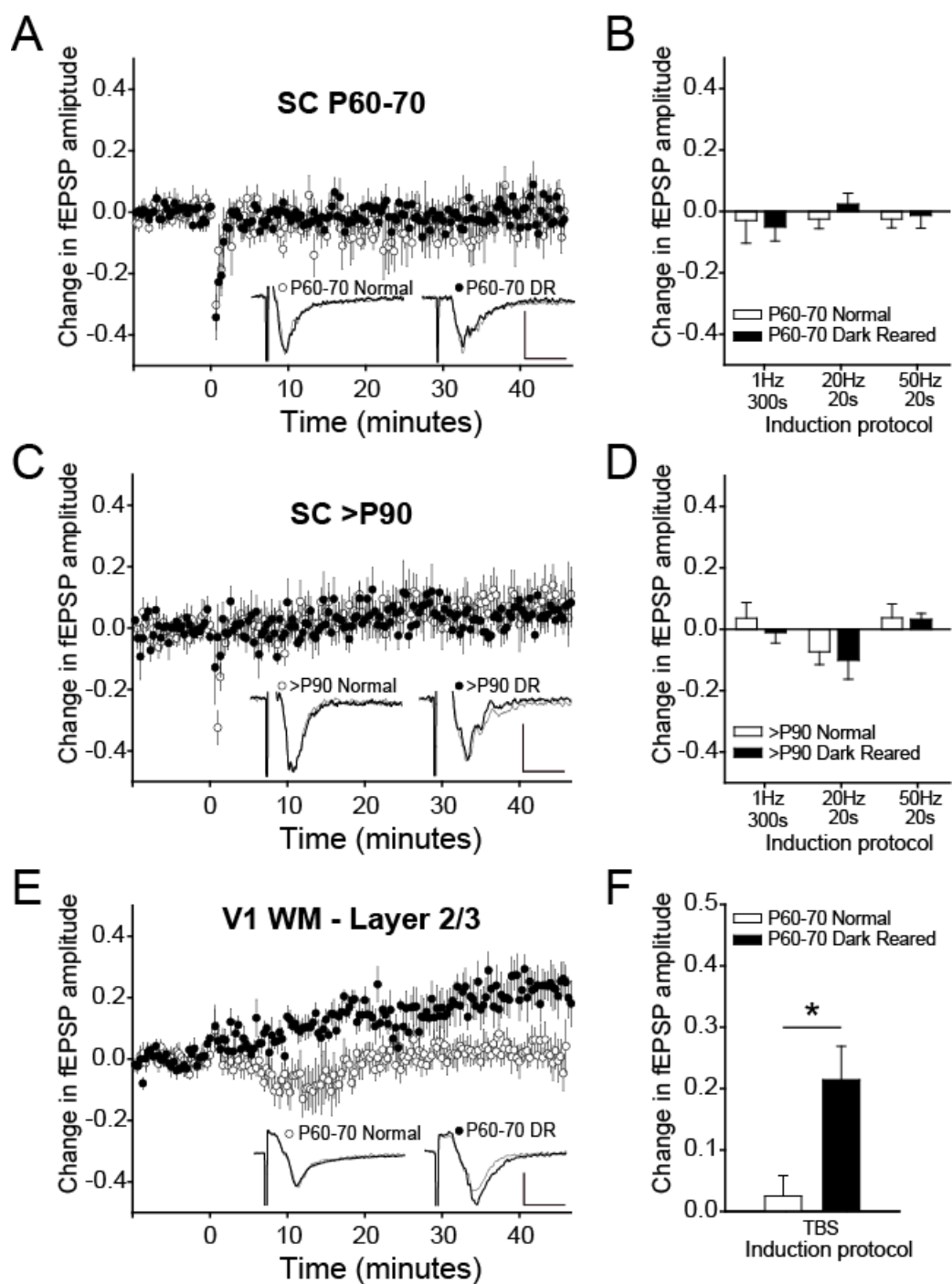


Figure 3.2. Long-term plasticity in SC is not affected by visual experience

A) fEPSPs were evoked at 20s intervals. After the fEPSP amplitude was stable for >10 minutes a 50Hz 20s stimulus was applied. There was no significant change in slices from normal or from DR animals between P60-70. Example traces are averages during 10 min baseline (thin gray) and 30-40 min after induction protocol (thick black). Scale bar 0.2 mV, 5 ms. B) Other induction protocols at this age also did not cause long-term plasticity. Data plotted are mean change from 30-40 min after induction stimulus normalized to 10 min baseline. C) There was also no significant change after a 50Hz 20s stimulus in slices from normal or DR animals >P90. Example traces and scale bar as in A. D) There were also no differences between slices from normal or DR animals using 3 other induction protocols. E) In contrast, in V1 WM-L2/3 LTP was induced in slices from DR animals but not in slices from normal animals. Example traces and scale bar as in A. F) TBS caused significantly more LTP in V1 slices from DR than from normally reared animals. *P < 0.05.

3.4.3 Visual experience prevents a DR-induced increase in paired pulse depression

Our first approach to studying short-term plasticity was to measure paired pulse ratio (PPR). Reduced inhibition in DR SC (Carrasco et al., 2011) could increase the probability of excitatory neurotransmitter release in SC, which could increase RF size by increasing evoked excitability. This experiment was designed to measure the level of short-term plasticity evoked by paired pulse stimulation as an assay for possible DR-induced changes in probability of neurotransmitter release. Decreased amplitude of the second pulse (PP2) relative to the first pulse (PP1), ($PPR = PP2 / PP1$) indicates paired pulse depression ($PPR < 1$), whereas an increase in PP2 indicates facilitation ($PPR > 1$). In the SC, paired pulse depression (PPD) occurs normally and is thought to be related to recognition of novel stimuli (Platt and Withington, 1997). Inhibition likely contributes to PPD in SC (Platt and Withington, 1997). DR SC has reduced GABAergic inhibition (Carrasco et al., 2011), as is typical of several systems after sensory deprivation (Gabbott and Stewart, 1987; Bakkum et al., 1991; Benevento et al., 1992; Benevento et al., 1995; Micheva and Beaulieu, 1995; Morales et al., 2002; Jiao et al., 2006; Kotak et al., 2008). Because inhibition is reduced by DR, we predicted an increase in the probability of neurotransmitter release and

that PPD would be reduced. To test whether this form of short-term plasticity is affected by visual experience, slices from normal and DR animals were stimulated by paired pulses with intervals ranging from 20 to 200 ms. The stimulus intensity was set to 25% of the maximal response that could be elicited in order to test depression in response to mild stimulation.

Contrary to our prediction, we found that PPD was increased in slices from DR animals. PPR was significantly lower (increased depression) in slices from DR animals, indicating a higher level of PPD (Two-way repeated measures ANOVA, $F(1,202) = 5.160$, $N = 50$, $P = 0.028$, Student's t-tests, $P < 0.05$ at 20, 100 and 150 ms intervals, Fig. 3.3A-B). The change in PPD was due to a weaker response to the second pulse in slices from DR animals, rather than a stronger response to the first pulse, because the first pulse was not affected by rearing condition (Two-way repeated measures ANOVA, $F(1,222) = 0.0261$, $N = 50$, $P = 0.872$). There was also a significant effect of inter-pulse interval on PPR (Two-way repeated measures ANOVA, $F(4,202) = 6.958$, $N = 50$, $P < 0.001$, Fig. 3.3A).

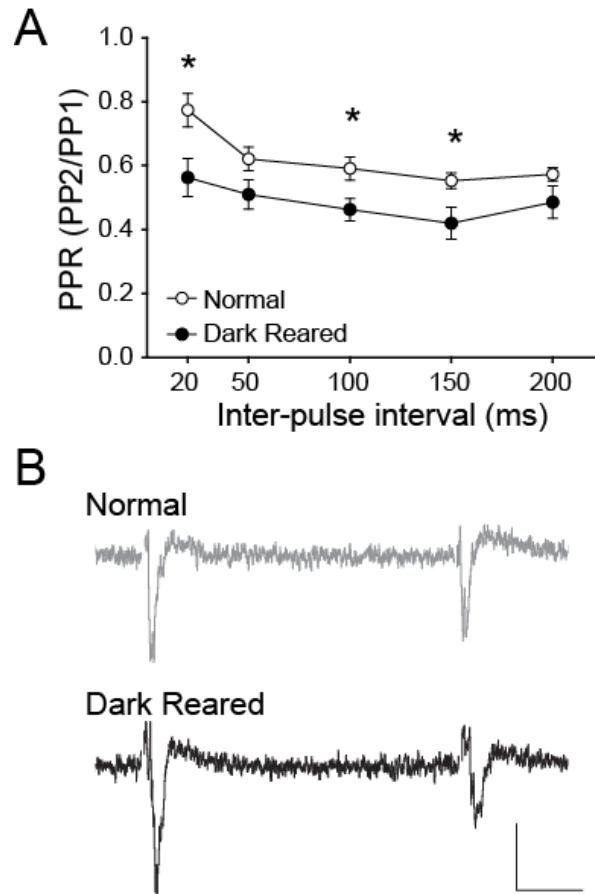


Figure 3.3. Lack of visual experience causes increase in PPD

A) DR animals have higher PPD (lower PPR), compared to normal animals. * $P < 0.05$. B) Examples of PPD in a slice from a normal (gray) and a DR (black) animal. Note that the response to the second pulse (PP2) of the DR trace is much smaller than the response to the first pulse (PP1), whereas in the normal trace PP2 is only slightly smaller than PP1. Stimulus artifacts are omitted for clarity. Scale bar 0.1 mV, 10 ms.

3.4.4 *GABA_BR* function underlies PPD, but is not directly affected by visual experience

GABA_BRs could underlie PPD through either presynaptic inhibition of excitatory neurotransmitter release or postsynaptic inhibition that is activated by the first stimulus pulse and remains during the second stimulus pulse. GABA_BRs are metabotropic receptors that hyperpolarize neurons with a slow onset and long duration (Benardo, 1994) by increasing K⁺ channel conductance and/or decreasing

Ca²⁺ channel conductance (Alger and Nicoll, 1982; Benardo, 1994; Chalifoux and Carter, 2011). SC expresses GABA_BRs at an extremely high level relative to other areas of the brain (Bowery et al., 1984) at both pre- and postsynaptic sites (Endo and Isa, 2002). A deprivation-induced increase in GABA_BR function could underlie the increased PPD observed in slices from DR animals. If slices from DR animals are more sensitive to GABA_BR agonists and antagonists than slices from normal animals, the hypothesis would be supported.

We first tested the effect of the GABA_BR antagonist CGP55845 on PPD. For this and all subsequent experiments, the inter-pulse interval was 100 ms and the stimulation intensity was set to 75% of the maximum response that could be elicited from each slice, in order to avoid a floor effect (saturated PPD). At this stimulation intensity, the difference in PPD between rearing conditions was not always apparent, which was not unexpected, given the known stimulus intensity dependent dynamics of PPD (Platt and Withington, 1997; Kim and Alger, 2001). Application of 3 μM CGP55845 significantly decreased PPD (increased PPR) in slices from both rearing conditions (paired t-tests, Normal PPR before CGP55845: 0.652 ± 0.0269 to Normal PPR during 3 μM CGP55845: 0.887 ± 0.0354 , $n = 14$, DR PPR before CGP55845: 0.662 ± 0.0390 to DR PPR during 3 μM CGP55845: 0.920 ± 0.0313 , $n = 10$, $P < 0.001$, Fig. 3.4A). However, the ability of CGP55845 to reduce PPD was not significantly different between slices from normal and DR animals (Student's t-test, Normal: 37.5 ± 5.96 % increase in PPR, $n = 14$ vs. DR: 42.2 ± 8.71 % increase in PPR, $n = 10$, $P = 0.649$, Fig. 3.4B-C). In addition, the effect of CGP55845 on the amplitude of PP1 was not significantly different between rearing conditions (Normal: -0.353 ± 0.0237 mV, Normal with CGP 55845: -0.435 ± 0.0382 mV, $n = 16$; DR: -0.370 ± 0.0199 mV, $n = 16$, DR with CGP55845: -0.475 ± 0.0402 mV, $n = 13$, Student's t-test comparing effect between treatment conditions, $P = 0.515$).

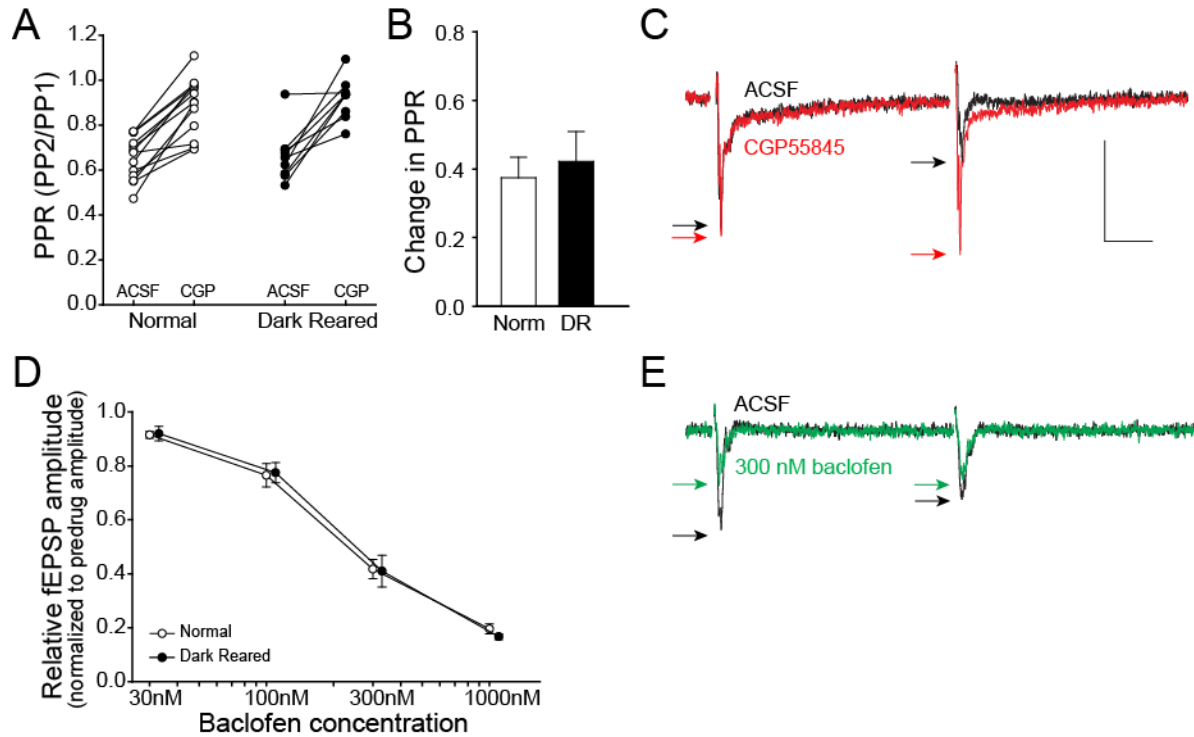


Figure 3.4. GABA_BR function is required for PPD, but is not directly affected by visual experience

A) Application of the GABA_BR antagonist CGP55845 (3 μ M) decreased PPD in slices from both normal and DR animals. This panel shows that GABA_BR-mediated inhibition underlies PPD in SC. B) The effect of CGP55845 on PPD ((gabazine – ACSF) / ACSF) was not significantly different between rearing conditions. C) Example trace showing the effect of CGP55845. The largest effect is the increase in PP2, which decreases PPD (increase in PPR). Black trace is pre-drug and black arrows point to the peaks. Red trace is during bath application of CGP55845, and red arrows point to the peaks. Scale bar 0.2 mV, 20 ms. D) Application of the GABA_BR agonist baclofen reduced the fEPSP amplitude of the response to the first pulse, but the effect was not significantly different between rearing conditions. E) Baclofen decreased PPD (green trace/arrows, increased PPR). In contrast to the effect of CGP55845, baclofen affected PP1 more than PP2, suggesting that PP2 is nearly maximally affected by GABA_BR-mediated inhibition under normal (no drug) conditions. Stimulus artifacts are omitted for clarity. Scale bar as in C.

Second, we tested the effect of the GABA_BR agonist (*RS*)-baclofen on PPD. Increasing concentrations of baclofen reduced the fEPSP amplitude of PP1 monotonically, but there was no difference in response amplitude between slices from normal and DR animals (Two-way repeated measures ANOVA, $F(1,55) = 0.0323$, $N = 16$, $P = 0.860$, Fig. 3.4D-E), nor was there a difference in the effect of baclofen on PPR between treatment groups (Normal: predrug PPR: 0.597 ± 0.0453 , 30 nM PPR: 0.611 ± 0.0631 , 100 nM PPR: 0.691 ± 0.0472 , 300 nM PPR: 0.971 ± 0.0490 , $n = 9$; vs DR: predrug PPR: 0.550 ± 0.0332 , 30 nM PPR: 0.598 ± 0.0270 , 100 nM PPR: 0.677 ± 0.0311 , 300 nM PPR: 0.896 ± 0.0764 , $n = 7$; Two-way repeated measures ANOVA, $F(1,57) = 0.221$, $P = 0.645$, $N = 16$).

These experiments show that, although GABA_BR-mediated inhibition underlies PPD in SC, there is no apparent effect of visual experience on GABA_BR sensitivity or on the degree of tonic GABA_BR-mediated inhibition in SC. Decreasing GABA_BR-mediated inhibition with CGP55845 relieves the robust inhibition of PP2, but also increases the amplitude of PP1. This indicates that PP1 is slightly inhibited under normal conditions (without drug).

3.4.5 Reduced GABA_AR function underlies increased PPD in slices from DR animals

Although GABA_BR function appears to be equivalent in slices from normal and DR animals (cf. Fig. 3.4), it is possible that DR-induced decreases in GABA_AR efficacy could lead to changes in GABA release. GABA_ARs are the largest contributor to fast synaptic inhibition in the SC. We previously showed that GABA_AR agonists and antagonists affect visual response and RF size less in DR than in normally reared animals, suggesting that visual experience is necessary to maintain GABA_AR function (Carrasco et al., 2011). We hypothesized that reduced GABA_AR function in DR SC could disinhibit GABAergic neurons, which would cause increased GABA release and, in turn, could increase GABA_BR-mediated PPD (Fig. 3.5A). This increased GABA release would enhance the GABA_BR mediated inhibition of PP2, and could underlie the increased PPD in slices from DR animals (Fig. 3.5B).

To test whether a DR-induced reduction in GABA_AR function underlies increased PPD, the GABA_AR antagonist SR-95531 (gabazine) was bath-applied on slices from normal animals. GABA_AR

blockade with 10 μM gabazine caused a significant increase in PPD (decrease in PPR) in slices from both normal and DR animals (paired t-tests, Normal pre-gabazine PPR: 0.568 ± 0.0340 compared to Normal PPR during 10 μM gabazine: 0.293 ± 0.0398 , $n = 14$, $P < 0.001$; DR PPR pre-gabazine: 0.550 ± 0.0383 compared to DR PPR during 10 μM gabazine: 0.398 ± 0.0538 , $n = 11$, $P = 0.001$, Fig. 3.5C). However, this effect was significantly greater in slices from normal animals than in slices from DR animals (Student's t-test, Normal: $50.3 \pm 5.08\%$ decrease in PPR, $n = 14$ vs. DR: $29.6 \pm 6.04\%$ decrease in PPR, $n = 11$, $P = 0.015$, Fig. 3.5D). Thus, reducing GABA_AR function in slices from normal animals mimicked the effect of DR on PPD (cf. Fig. 3.3), arguing that reduced GABA_AR function such as occurs in DR SC (Carrasco et al., 2011) is likely to underlie increased PPD.

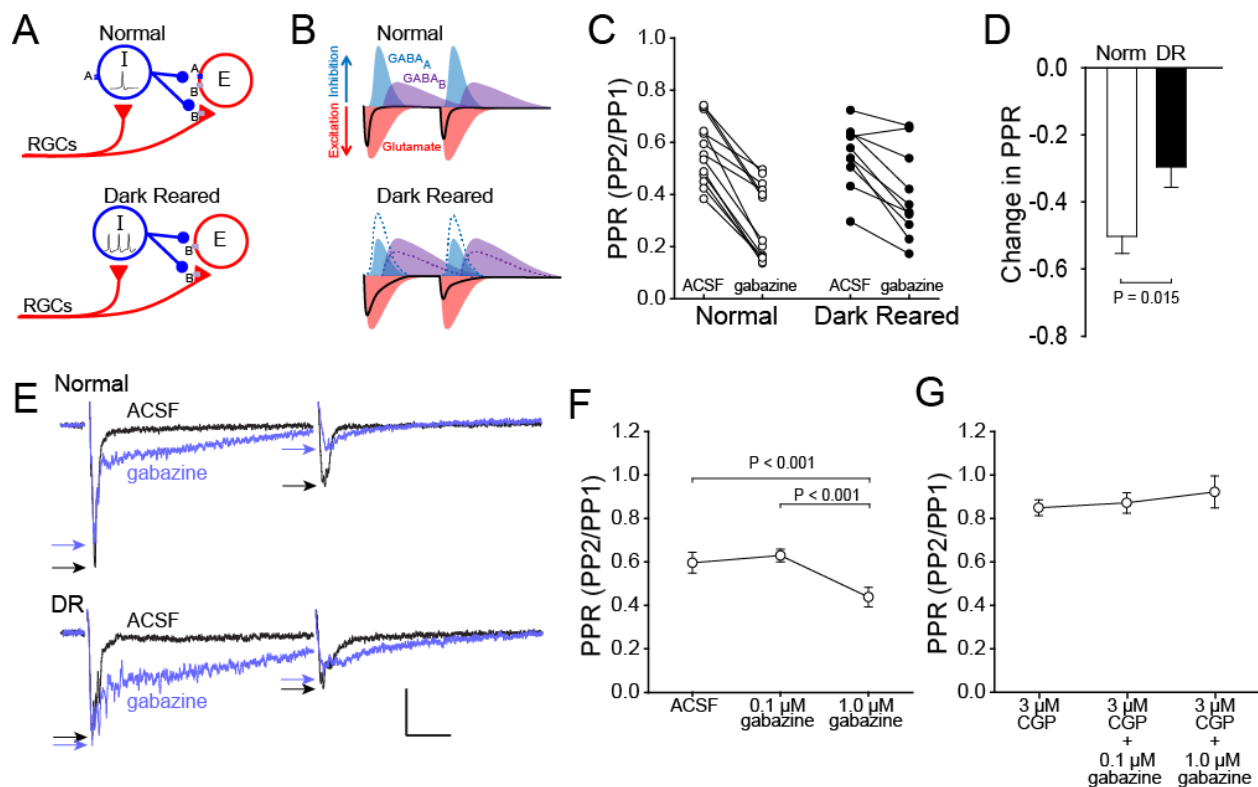


Figure 3.5. Reduced GABA_AR function underlies increased PPD in slices from DR animals

A) Hypothetical circuit model showing that when GABA_ARs are reduced by DR (or blocked) the inhibitory neurons (I) are disinhibited and GABA release increases, resulting in increased GABA_BR-mediated inhibition of excitatory neurons (E). Triangles are excitatory, circles are inhibitory. B) Model

showing how reduced GABA_AR function, increased GABA release, and increased GABA_BR-mediated inhibition could increase PPD in slices from DR animals. Increased GABA release enhances GABA_BR-mediated inhibition of excitatory neurons (E), which increases the fEPSP duration, and increases inhibition of PP2 (dotted lines are normal condition for comparison). C-D) The GABA_AR antagonist gabazine (10 μM) reduced the PPR significantly more in slices from normal animals (50.3 ± 5.08 % decrease in PPR) than in slices from DR animals (29.6 ± 6.04 % decrease in PPR). E) Gabazine caused a large increase in the duration of the fEPSP in slices from both normal and DR animals, which is likely caused by disinhibition of both excitatory and inhibitory neurons and increased duration of evoked responses. Stimulus artifacts are omitted for clarity. Scale bar 0.2 mV, 20 ms. Arrows indicate peaks of fEPSPs. F) 1 μM gabazine was sufficient to increase PPD (decrease PPR) in slices from normal animals. Thus, reducing GABA_AR function in slices from normal animals mimicked the increased PPD seen in slices from DR animals (cf. Fig. 3.3). G) Blockade of GABA_BRs prevented the increase in PPD caused by 1 μM gabazine, supporting the model in which reduced GABA_AR function increases PPD by increasing inhibitory neuron output, and in turn, increasing GABA_BR-mediated inhibition.

3.4.6 DR-induced reduction in GABA_AR function controls PPD via GABA_BR-mediated inhibition

GABA_AR blockade with gabazine increases evoked activity of both GABAergic and non-GABAergic neurons in SC (Kaneda et al., 2008). GABA_AR blockade also had a marked effect on the fEPSP duration in slices from normal and DR animals. The area of the fEPSP - a measure of duration calculated from peak of the fEPSP to 100 ms after the peak (Georgiou et al., 2010) - increased several fold in slices from both normal and DR animals, but there was no difference in the effect of gabazine between treatment groups (Mann-Whitney Rank Sum, Normal: 4.22 median fold increase, n = 15; DR: 3.99 median fold increase, n = 11, P = 0.396, examples shown in Fig. 3.5E). Increased evoked activity of GABAergic neurons would increase GABA release that would in turn cause increased activation of GABA_AR and GABA_BRs. GABA_BRs are more highly expressed in SC than GABA_ARs (Bowery et al., 1984) and are thought to have a greater effect on PPD because of their presynaptic locus (in addition to

postsynaptic expression). Here we test the hypothesis that DR-induced reduction of GABA_ARs causes increased PPD via disinhibition of GABA release and increased GABA_BR-mediated inhibition. This hypothesis predicts that GABA_BR-mediated inhibition is necessary for the increase in PPD caused by GABA_AR blockade with gabazine. Bath application of 1 μ M gabazine was sufficient to cause an increase in PPD in slices from normal animals (One-way repeated measures ANOVA, $F(2,14) = 40.012$, $n = 5$, $P < 0.001$; Tukey's tests, predrug (ACSF) PPR vs. 1 μ M gabazine PPR, $P < 0.001$, Fig. 3.5F). Although CGP55845 significantly increased PPR (decreased PPD) as expected (One-way repeated measures ANOVA, $F(3,23) = 22.089$, $n = 6$, $P < 0.001$; Tukey's test, Predrug (ACSF) PPR: 0.509 ± 0.0344 , vs. 3 μ M CGP55845 PPR: 0.849 ± 0.0367 , $P < 0.001$), blocking GABA_BRs with 3 μ M CGP55845 prior to applying gabazine prevented the increase in PPR (Tukey's tests, 3 μ M CGP55845 PPR vs. 3 μ M CGP55845 and 0.1 μ M gabazine PPR, $P > 0.05$; 3 μ M CGP55845 PPR vs. 3 μ M CGP55845 and 1.0 μ M gabazine PPR, $P > 0.05$, Fig. 3.5G).

Taken together, these experiments suggest that the reduced GABA_AR function seen in DR animals could lead to increases in the activity of GABAergic interneurons, which in turn could increase PPD by enhancing GABA_BR-mediated inhibition (Fig. 3.5B). This increased GABA_BR-mediated inhibition increases depression of the second pulse through pre- and/or post-synaptic inhibition (Fig. 3.5A).

3.4.7 Recovery from train-induced STD is mediated by GABA_BRs, maintained by visual experience, and reduced by DR

The PPD study revealed a major contribution of GABA_BRs in STD, but it is difficult to imagine a situation where a natural visual stimulus would stimulate the SC in such a way. During visual stimulation with moving spots of light, SC neurons are strongly activated with trains of high frequency impulses (Cirone and Salt, 2001; Razak and Pallas, 2005). Thus, in a second set of experiments we presented trains of current pulses and tested the time course of recovery from the resulting STD. A conditioning stimulus

consisting of a train of 10 pulses at 100 Hz is known to induce profound STD that recovers after about 1 s (Kaneda et al., 2008).

Test pulses delivered at 100 - 1200 ms intervals after the end of the conditioning stimulus train were used to measure the strength and degree of recovery of the train-induced STD (Fig. 3.6A). The stimulation intensity of the train and test pulses was set to 75% of the maximal response of each slice for this study, and the fEPSP amplitudes evoked by the test pulses were normalized to the first conditioning pulse. Slices from DR animals were less depressed after the conditioning stimulus than the slices from normally reared animals 100, 200 and 400 ms after the conditioning stimulus (Two-way repeated measures ANOVA, $F(1,149) = 5.064$, $N = 30$, $P = 0.032$, Fig. 3.6B)

Informed by our finding that GABA_BR inhibition underlies PPD in SC, we tested whether or not GABA_BR-mediated inhibition also underlies the STD caused by train stimulation. GABA_BR-mediated inhibition could underlie this form of STD because STD in this paradigm is strongest at approximately 100 ms after the conditioning stimulus and lasts for about 1 s, following the time course of action of GABA_BR-mediated inhibition (Benardo, 1994). If GABA_BRs underlie train-induced STD, then reducing GABA_BR-mediated inhibition will reduce the STD.

Indeed, in both slices from normal and DR animals, GABA_BR antagonist CGP55845 (3 μ M) almost completely blocked STD from occurring after the 100 Hz train stimulus (Two-way repeated measures ANOVA, Normal: $F(1,124) = 209.970$, $n = 7$, $P < 0.001$; DR: $F(1,84) = 46.710$, $n = 5$, $P < 0.001$, Fig. 3.6C-D). The remaining STD observed during GABA_BR blockade is likely caused by GABA_BR-independent mechanism of STD (Lambert and Wilson, 1994). There was no difference between slices from normal and DR animals in STD during CGP55845 application (Two-way ANOVA, $F(1,59) = 0.704$, $N = 12$, $P = 0.405$, Fig. 3.6C).

Taken together, these studies indicate that recovery from train-induced STD in SC is mediated by GABA_BRs and is altered by visual experience. Thus, although DR increases PPD (cf. Fig. 3.3), it decreases the duration of STD caused by a train of pulses. Indeed, a higher probability of

neurotransmitter release in the disinhibited slices from DR animals could cause GABA to be depleted more quickly, which could contribute to reduced maximal STD duration.

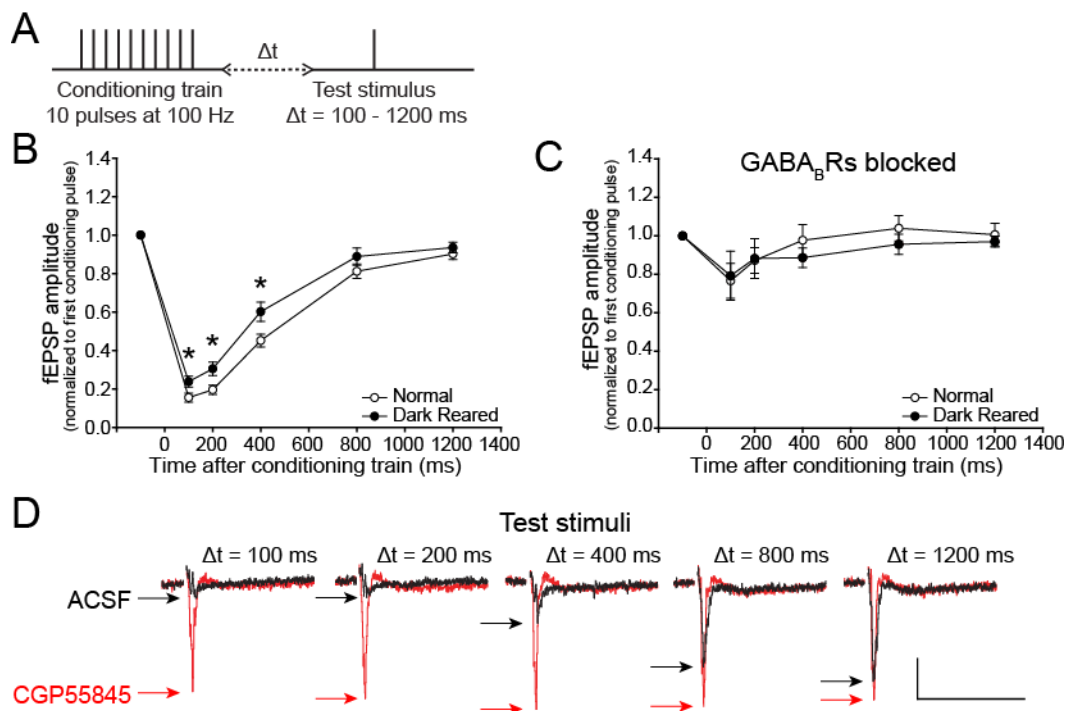


Figure 3.6. Rapid recovery from train-induced STD is maintained by visual experience, is reduced by DR, and is mediated by GABA_BR inhibition

A) A 10 pulse conditioning stimulus train delivered at 100Hz was followed by test stimuli presented at either 100, 200, 400, 800 or 1200 ms to measure the extent and recovery of STD. B) Slices from normally reared animals were significantly more depressed by the conditioning stimulus than slices from DR animals. Thus, although DR increased STD after a single stimulus (PPD, cf. Fig. 3.3), DR decreased STD after the train stimulus. * $P < 0.05$. C) 3 μ M CGP55845 blocked STD from occurring in slices from both normal and DR animals, but there were no significant differences in the extent of the effect between groups. This shows that recovery from the train-induced STD is strongly inhibited by GABA_BR activity. D) Example of a single experiment, using a slice from a normal animal, showing that at short intervals after the conditioning stimulus the fEPSP is quite depressed. This depression is relieved when GABA_BRs

are blocked with CGP55845 (red traces). Stimulus artifacts are omitted for clarity. Scale bar 0.2 mV, 50 ms.

3.4.8 Reduced synaptically released GABA recapitulates the effects of DR on reduced train-induced STD

Although we found no effect of visual experience on GABA_BR function (cf. Fig. 3.4) we reasoned that reduced presynaptic GABA in SC cells could reduce stimulus evoked GABA_BR-mediated inhibition. Visual experience maintains GABA in SC neurons, which is reduced by DR (Carrasco et al., 2011). Here we tested whether reduced GABA in SC could recapitulate the reduced STD that we observed in slices from DR animals. We recorded the time-course of recovery from STD in normal slices as above, and then reduced GABA in two different ways.

In the first approach, we utilized the pattern of GABA_CR expression in SC. GABA_CRs are ionotropic chloride channels similar to GABA_ARs that are preferentially expressed by inhibitory neurons and have a higher affinity for GABA than do GABA_ARs and GABA_BRs (Platt and Withington, 1998; Pasternack et al., 1999; Schmidt et al., 2001). Thus, when low concentrations of GABA are bath applied, inhibitory neurons are inhibited, which reduces the amount of synaptically released GABA and increases fEPSP amplitude. We applied 300 μ M GABA, a concentration that binds to the high affinity GABA_CRs and reduces GABA release, which we inferred by observing an increase in the fEPSP amplitude ($124.0 \pm 7.57\%$). Reducing synaptically released GABA in this way caused the predicted reduction in STD (Two-way repeated measures ANOVA, $F(1,119) = 5.803$, $P = 0.035$, $N = 12$, Fig. 3.7A). The time constant of recovery from STD (time to reach $1 - e^{-1} = 63.2\%$ recovery) was also significantly reduced by 300 μ M GABA (paired t-test, $P = 0.006$, $N = 10$, Fig. 3.7B). Recovery is likely more rapid in DR slices because there was less STD 100 ms after the conditioning train, although we cannot rule out other mechanisms such as differences in vesicle filling rates. This experiment suggests that reduced GABA, as occurs in DR SC (Carrasco et al., 2011), may underlie reduced STD caused by train stimulation. While unlikely, it is possible that constant application of even this low concentration of GABA could cause GABA_BR

desensitization that could contribute to the effect seen. Thus, we used a second approach to circumvent this alternative hypothesis.

Although unlikely, it is possible that constant application of even this low concentration of GABA could cause GABA_BR desensitization that could contribute to the effect seen. Thus, we used a second approach to test this alternative hypothesis. In this second approach, we reduced GABA by applying a GABA depleting agent, isonicotinic acid hydrazide (isoniazid). Isoniazid inhibits pyridoxal phosphate, the cofactor of the GABA synthesizing enzyme glutamic acid decarboxylase (GAD), and has been used to reduce GABA in acute brain slices (De Koninck and Mody, 1997; Carta et al., 2008). 1 mM isoniazid had no apparent effect, and 10 mM isoniazid instead reduced the fEPSP amplitude ($87.0 \pm 5.07\%$) and caused single-unit spikes to appear, indicating severely reduced inhibition. Bath application of 3 mM isoniazid caused an increase in the fEPSP amplitude ($109.3 \pm 5.94\%$, Fig. 3.7C). 3 mM isoniazid reduced the duration of STD (Two-way repeated measures ANOVA, significant interaction between time after train and isoniazid concentration, $F(8,104) = 4.370$, Tukey's t-test, significant effect ($P < 0.05$) of 3 mM isoniazid at 100, 200 and 800 ms latencies, $N = 6$, Fig. 3.7C). The time constant of recovery from STD was also significantly reduced by 3 mM isoniazid (One-way repeated measures ANOVA, $P = 0.026$, Tukey's test, ACSF vs. 3 mM isoniazid, $n = 6$, $P = 0.021$, Fig. 3.7D), which is probably due to reduced depression 100 ms after the conditioning train in the slices from DR animals. Taken together, these experiments support the hypothesis that reduced GABA in DR SC is responsible for the faster than normal recovery from STD, and that maintenance of STD through visual experience depends on maintenance of presynaptic GABA.

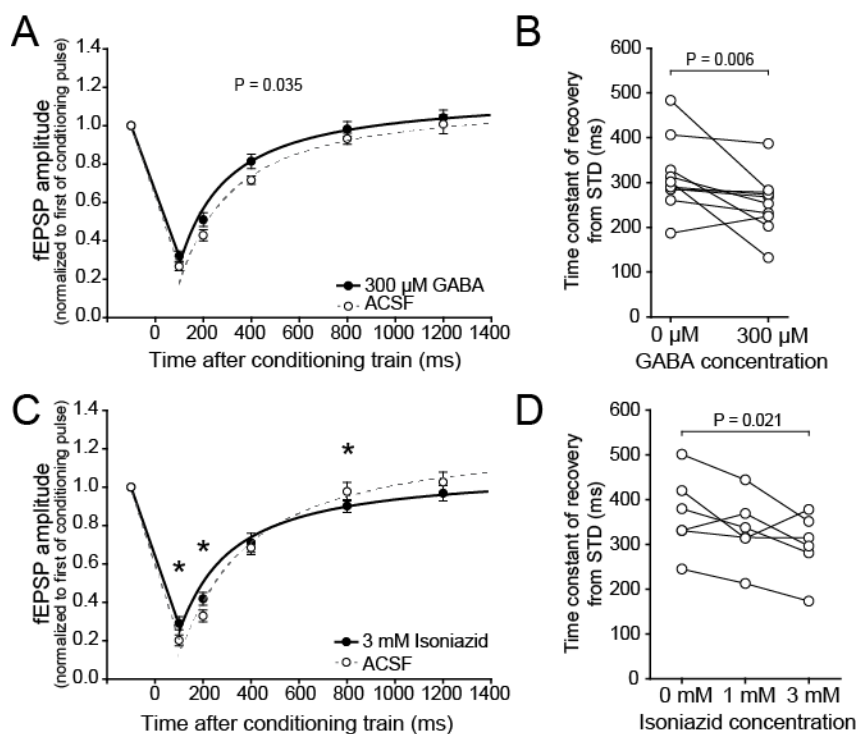


Figure 3.7. Reducing synaptically released GABA recapitulates reduced train induced STD seen in DR slices

A) 300 μ M GABA significantly reduced STD induced by the 10 pulse, 100Hz conditioning train (cf. Fig. 3.6A) (One-way repeated measures ANOVA ($P = 0.035$)). Exponential fits are shown from 100 – 1400 ms after the conditioning train for ACSF (dashed gray line) and 300 μ M GABA (black line). B) Exponentials were fit to the recovery from STD of each slice before and after GABA application. 300 μ M GABA caused a significant decrease in the time constant of recovery. C) 3 mM isoniazid reduced GABA synthesis and significantly reduced the train-induced STD at the 100 and 200 ms time points. $*P < 0.05$. Exponential fits as in A. D) The time constant of recovery from STD reached significance ($P = 0.021$) at 3 mM isoniazid.

3.4.9 How does STD affect RF size?

The classical definition of a RF is the area of the visual field within which a stimulus causes a neuron to fire action potentials. STD affects excitability and action potential firing and thus necessarily

affects RF size. V1 RFs are known to change size in reaction to visual stimulation (Pettet and Gilbert, 1992) and contrast levels (Kapadia et al., 1999; Sceniak et al., 1999). Here we use a RF model to investigate how STD, which is maintained by visual experience, contributes to the maintenance of refined RFs, and how DR, which reduces the magnitude and duration of train-induced STD, could contribute to enlarged RFs.

We showed increased PPD and decreased train-induced STD in slices from DR animals. The train stimulus more closely resembles the barrage of action potentials generated by natural vision than does a single stimulus pulse, thus we modeled the effect of reductions in train-induced STD rather than PPD on RF size. To investigate how STD affects RF size we constructed a difference of Gaussians (DOG) model of RFs (Rodieck, 1965). The DOG model results in a “Mexican hat” response function ‘ R ’ by subtracting the inhibitory response Gaussian from the excitatory response Gaussian.

$$R = K_e e^{-\left(\frac{2x}{a}\right)^2} - K_i e^{-\left(\frac{2x}{b}\right)^2}$$

K_e and K_i are the peaks and a and b are the space constants of the excitatory and inhibitory Gaussians, respectively. The SC responds best to visual stimuli that are smaller than the excitatory RF due to strong within-RF inhibition. We based the normal RF Gaussians in our model on size tuning data from Syrian hamster SC (Razak and Pallas, 2006), optimizing K_e , K_i , a and b for best fit using the following equation, as previously described (DeAngelis et al., 1994; Sceniak et al., 1999; Chen et al., 2013).

$$R(y) = K_e \int_{-y/2}^{y/2} e^{-\left(\frac{2x}{a}\right)^2} dx - K_i \int_{-y/2}^{y/2} e^{-\left(\frac{2x}{b}\right)^2} dx$$

As expected, inhibition is strong- more than half as strong as the peak of excitation- ($K_i = 0.52 * K_e$) and the width of inhibition is more than one and a half times that of excitation ($b = 1.66 * a$). The DOG function using these values is plotted in Fig. 3.8A.

To model the effect of STD on RF size, we reduced the amplitude of the excitatory Gaussian K_e . Figure 3.8B shows several DOGs plotted with varying levels of depression from 0 (K_e - 0%) to 25% (K_e - 25%), in 5% intervals. RF size was calculated as the width of the DOG at 20% of the peak (indicated by a horizontal line), ignoring responses below zero. The 20% level reflects how SC RFs were measured *in vivo* (Carrasco et al., 2005; Balmer and Pallas, 2013).

When depression reduced the peak of the excitatory response Gaussian K_e by a total of 25%, the RF width was reduced to 78% of its initial, pre-depression size. When depression is reduced, as is the case in DR SC, RF width does not shrink to the same extent. For example, when depression was only 10%, the RF width remained at 93% of its initial size (Fig. 3.8B). This shows that when depression is reduced the RF shrinks less than it does at higher levels of depression.

It is clear that DR reduces inhibition in the SC, thus we modeled the reduced inhibition to test whether it changes the effect of STD on RF size. Before altering depression, we reduced the peak inhibitory response K_i by 40%, which caused a large increase in initial RF size because the excitatory response was less opposed by inhibition (Fig. 3.8C). This reduced inhibition in DR SC is likely a major reason that RFs are enlarged (Carrasco et al., 2011). However, reducing inhibition also caused the STD of the peak excitatory response K_e to have less of an impact on RF size. For example, under DR conditions (reduced GABA), 25% depression now reduces the RF width to 91% of its normal value (compared to 78% under normal rearing conditions of more inhibition, as in B). Figure 3.8D plots the RF widths with different levels of depression. The RF width shrinks more when depression is higher. The black line represents RF widths from Fig. 3.8B. In addition, when K_i is reduced, as would be the case in DR SC (Fig. 3.8C), depression has less of an effect on the RF width (blue dashed line, RF widths from Fig. 3.8C). Figure 3.8E plots absolute RF size. Although reduced STD contributes to enlarged RFs, the decrease in inhibition (plotted as the blue dashed line) also has a marked effect on initial RF size, indicated by an upward shift (in the blue dashed line) (Fig. 3.8E).

Surround inhibition is thought to derive from feed-forward inhibition. This suggests that any STD of excitation would also cause reduced inhibition, due to decreased activation of feed-forward inhibition. However, as long as there is more STD of excitation than STD of inhibition, the RF size will reduce during the first seconds of stimulation. We are confident that there is more STD of excitation than STD of inhibition, because we see depression of the fEPSP, which is an excitatory signal (cf. Fig. 3.1). Future experiments measuring the effects of DR on depression of excitatory and inhibitory currents are necessary to add detail to this model.

In sum, this analysis supports the idea that the reduced STD in slices from DR animals during visually-evoked activity causes RFs to be larger due to increased excitability. The combination of reduced inhibition and reduced STD combine to prevent RF size from shrinking during the initial moments of visual stimulation.

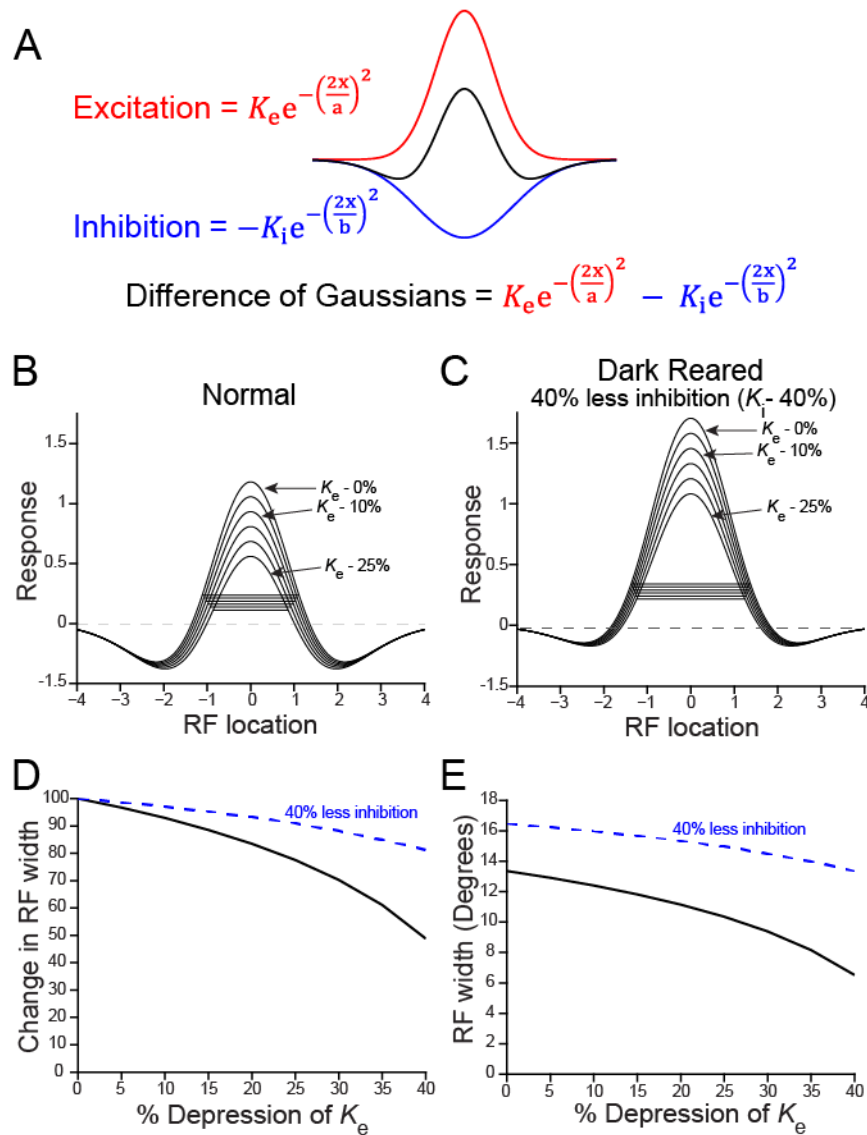


Figure 3.8. Reduced STD could contribute to enlarged RFs in DR animals

A) Difference of Gaussians (DOG) model of SC RFs. B) Depression was modelled as a reduction in K_e of 0 – 25%, in 5% intervals. The horizontal lines are the RF widths at 20% of the peak, corresponding to the method used for measuring RF widths *in vivo*. C) Lower levels of inhibition, as is seen in slices from DR animals, cause RFs to be larger. K_i was reduced by 40% to model the reduced inhibition caused by DR. The model supports the interpretation that reduced inhibition increases RF size. In addition, the RF

size in DR cases was less affected by depression than in normal cases, as can be seen in D. D) Change in RF width resulting from different levels of depression (RF widths from B, black line) and resulting from both depression and 40% reduced inhibition (data from C, blue dashed line). As the level of depression is increased, RF sizes shrink more. Reducing inhibition by 40% caused depression to have less of an effect on RF size (blue dashed line). E) Plotting absolute RF widths shows that the reduced inhibition increases RF size at all levels of depression (dashed blue line is shifted upward). Both increased depression and reduced inhibition caused by DR may contribute to RF enlargement.

3.5 Discussion

The goal of this study was to investigate the mechanisms of critical period closure in SC. We showed that in hamster SC, visual experience protects against deprivation-induced changes in short-term plasticity, but, unlike in V1, deprivation does not maintain long-term plasticity. Our data support a mechanism through which visual experience-dependent maintenance of GABA_AR function prevents metaplasticity of GABA_BR-mediated STD. DR increased PPD, likely by releasing inhibitory neurons from inhibition due to reduced GABA_AR function, thus increasing evoked GABA release onto GABA_BR of local SC neurons (Fig. 3.5 A-B). In addition, stimulation with a high frequency train of current pulses, more closely approximating natural vision, showed that maximal duration of STD is reduced in slices from DR animals (Fig. 3.6). Visual experience-dependent maintenance of GABA content may maintain maximal levels of visual stimulus-evoked STD in normally-reared animals. Our computational RF model shows that reduced STD during visual stimulation, which would maintain excitatory responses at a higher level, could explain the increased RF size in SC after DR.

3.5.1 *DR does not extend long-term plasticity in SC*

In primary visual cortex (V1), DR reduces inhibition, prolonging the age at which long-term synaptic plasticity occurs (Kirkwood and Bear, 1995; Kirkwood et al., 1995). DR causes reduced inhibition in SC as well, and could allow long-term plasticity and contribute to RF enlargement by

strengthening synapses on the outskirts of the excitatory RF. We were unable to induce long-term plasticity in SC slices from DR animals at the time of RF enlargement (P60-70) or once RFs were at their maximally enlarged state >P90, however. Thus, unlike in V1, in SC DR did not maintain the ability to induce long-term plasticity in acute slices, indicating that metaplasticity of LTP does not underlie DR-induced RF enlargement in the SC.

This experiment provides evidence that visual experience affects the retinocollicular and retinogeniculocortical pathways in different ways. This difference provides an opportunity to study differing mechanisms of development and plasticity in pathways that receive input from the same cells. Studies comparing plasticity in SC and V1 could elucidate differences in how experience affects midbrain and cortical visual circuits and identify the developmental processes underlying their distinct mechanisms.

3.5.2 Visual experience-dependent maintenance of GABAergic inhibition maintains GABA_BR activation

Reduced GABA_AR function that occurs in DR SC may lead to disinhibition of inhibitory interneurons that would enhance GABA release during a single stimulus. The disinhibited GABA release could cause more GABA_BR-mediated inhibition and thus increased PPD in DR animals. Longer duration stimulation, such as occurs during vision, leads to GABA depletion. This depletion likely occurs more rapidly in DR SC, because of reduced GABA content in these interneurons (Carrasco et al., 2011). This dysregulation of inhibition and STD could contribute to RF enlargement in DR SC.

3.5.3 GABA_BRs underlie STD in SC and are not affected by visual experience

Importantly, we report here that GABA_BRs almost completely underlie STD in SC, under both normal and deprived conditions. We showed that PPD increases as inter-pulse interval increases. This indicates that depression of PP2 depends on a delayed mechanism that lasts over 200 ms, such as a

metabotropic receptor signaling, rather than vesicle depletion. GABA_BRs fit this pattern (Chalifoux and Carter, 2011) whether operating through pre- or postsynaptic inhibition (Endo and Isa, 2002).

GABA levels and effectiveness of GABA_ARs in SC are reduced by DR (Carrasco et al., 2011), but little is known regarding the activity-dependent regulation of GABA_BR expression in SC. We did not find differences in sensitivity to GABA_BR agents between slices from normal and DR animals. GABA_BR expression is reduced by TTX blockade of retinal signaling in monkey LGN (Muñoz et al., 1998) and V1 (Muñoz et al., 2001), but TTX treatment is not directly comparable to DR, because it blocks both spontaneous and light-evoked activity. If DR causes reduced GABA_BR function in V1 but not in SC, it could explain differences in mechanisms of experience-dependent plasticity between cortical and midbrain visual areas. Comparing visual experience-dependent regulation of GABA_BRs between SC and V1 is necessary to test this prediction.

3.5.4 Reduced STD caused by high frequency train stimulation could contribute to RF enlargement in DR SC

The finding that high frequency train stimulation evokes less STD in slices from DR animals than normal animals led us to test how STD could affect RF size in a difference of Gaussians (DOG) RF model. In short, reduced STD in DR SC will yield higher than normal excitability during visual stimulation. Higher excitability that is not offset by higher inhibition would increase RF size. The DOG model was first applied to retina (Rodieck, 1965; Enroth-Cugell and Robson, 1966), but has also been used for modeling RFs in V1 (DeAngelis et al., 1994; Sceniak et al., 1999), frontal eye fields (Cavanaugh et al., 2012), and LGN (Dawis et al., 1984; Cai et al., 1997) and is a good first approximation to understanding center-surround RFs in general. Our RF model predicts how RF size could be affected by visual stimulus properties. The model suggests that high STD contributes to small RFs (normal) and low STD contributes to larger RFs (DR).

In an *in vivo* study in rat SC, iontophoresis of GABA_BR agents did not affect the size of RFs measured by varying stimulus sizes (Binns and Salt, 1997), which initially appears to be at odds with our

hypothesis. Iontophoresis likely affects receptors on the soma of the recorded cell and to a lesser extent its processes and nearby cells, whereas our bath-applied drugs may have affected somata and processes more uniformly. It is possible that for the drugs to affect STD, they need to affect presynaptic receptors on the retinocollicular afferents that make contact with the dendrites of the SC neurons, which may be too distal to be affected by iontophoresis.

3.5.5 Visual experience-dependent changes in STD could affect sensory processing in SC

The DR-induced increase in PPD suggests an increase in the probability of neurotransmitter release, which would likely increase sensitivity to light. This could be an advantage to an animal born into a dark environment or with visual pathologies such as cataract. However, there are several apparent tradeoffs for this increased sensitivity to light. The first is increased RF size, caused by DR-induced changes in STD and reduced inhibition, which would reduce visual acuity. If PPD is an underlying mechanism of novel stimulus detection, as has been suggested (Platt and Withington, 1997), then DR animals may have difficulty identifying novel stimuli, beyond that associated with low visual acuity alone. With reduced STD, slowly moving stimuli that cause slower spiking may not be perceived by SC due to disrupted gain control (Abbott et al., 1997) or temporal filtering (Fortune and Rose, 2001). Velocity tuning and size tuning are controlled by inhibition in SC (Razak et al., 2003; Razak and Pallas, 2005, 2006, 2007) and would likely be affected by changes in STD. Direction tuning is also mediated by STD, in V1 (Chance et al., 1998) and in the midbrain of weakly electric fish (Chacron et al., 2009). Sensory deprivation may be an experimental paradigm that could be used to test the role of STD in these properties of sensory processing.

3.5.6 Experience-dependent changes in STD vary between synapses and sensory areas

Sensory experience is necessary to decrease the STD of inhibition (iSTD) that is present during development at the layer 4 to 2/3 synapse in V1 (Jiang et al., 2005; Jiang et al., 2010) and auditory cortex (Takesian et al., 2010). Thus, visual experience causes inhibition to maintain its strength during stimulus

trains. Sensory deprivation causes inhibition to depress more (higher iSTD) than it would under normal rearing conditions during repeated stimulation. Increased iSTD in DR V1 may be due to the DR-induced reduction of GABAergic inhibition (Gabbott and Stewart, 1987; Bakkum et al., 1991; Benevento et al., 1995; Morales et al., 2002). As in DR V1, iSTD is increased in GAD65 knockout mice (Choi et al., 2002), indicating that the strength of inhibition weakens during stimulus trains under conditions of reduced GABA. This weakening of inhibition during stimulus trains may cause the reduced STD of fEPSPs that occurs in these mice (Fagiolini and Hensch, 2000). If, as reported in V1 and in auditory cortex, inhibition is maintained during train stimulation (low iSTD) in normal SC and inhibition weakens during train stimulation (higher iSTD) in DR SC, then this change in iSTD could mediate the reduced STD of fEPSPs in DR SC. Investigation of iSTD on a single neuron level in SC is necessary to test these predictions.

3.5.7 Dysregulation of inhibition and short-term plasticity in psychiatric disorders

Dysregulation of inhibition can lead to altered short-term plasticity which, depending on the synapse, can adversely affect sensory and cognitive processing (Abbott and Regehr, 2004). These changes in processing may contribute to psychiatric disorders, including schizophrenia and neurodegenerative diseases (Arguello and Gogos, 2012). Short-term plasticity is affected by environmental factors such as brain injury (Li et al., 2005), early life seizures (Hernan et al., 2013), and hearing loss (Takesian et al., 2010). Preventing dysregulation of inhibition from occurring, or intervening with therapies that affect inhibitory plasticity, may ameliorate disrupted short-term plasticity and provide a therapeutic approach to some aspects of pervasive psychiatric disorders.

3.6 Acknowledgements

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4 DISCUSSION

In this dissertation, I investigated the role of visual experience in the development and plasticity of the visual pathway. Contrary to a widely held view, visual experience is not necessary for refinement of RFs in primary visual cortex (V1). In both SC and V1, RFs refine by P60, but enlarge by P90 with chronic DR. One week of visual experience was sufficient to prevent RF enlargement in SC and V1. Normal sensory experience prevents RF plasticity in mature circuits by maintaining GABAergic and GABA_BR-dependent short-term synaptic plasticity.

4.1 Model of RF plasticity

Experience-independent and experience-dependent RF plasticity can be represented by a ‘stability landscape’ in which a ball rolls along a three-dimensional surface (Fig. 4.1). This stability landscape metaphor was first used to describe how genes and environment interact during development by Conrad Waddington (Waddington, 1957) and has been applied to critical period plasticity (Knudsen, 2004).

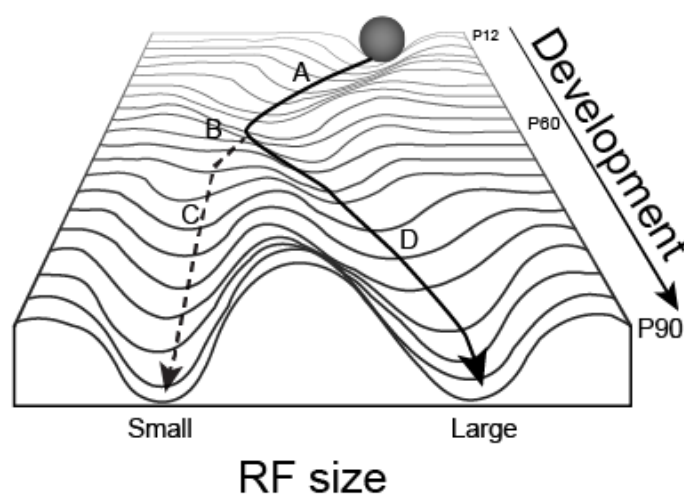


Figure 4.1. Stability landscape describing RF refinement and plasticity.

The ball starts on the right side of the landscape, which represents large, unrefined RFs. The ball rolls forward during development. Its movement leftward, toward small RFs, represents refinement. RF refinement occurs independent of visual experience, is not easily perturbed, and is therefore represented by a valley, 'A'. In both SC and V1, a profound perturbation is required to deviate from the trajectory of RF refinement, such as activity blockade or disruption of correlated spontaneous activity. The valley becomes less deep as development approaches P60, after which time RFs begin to expand in the absence of visual experience in both SC and V1. At this point, visual experience is necessary to force the ball over a hill, 'B', into the valley of RF maintenance, 'C'. Without this force of visual experience, the ball rolls to the right along the valley that leads to enlarged RFs, 'D'. After P90, no perturbation is sufficient to cause refinement or enlargement of RFs and development has ended.

The synaptic mechanisms that underlie visual experience dependent RF maintenance are pictured in Figure 4.2.

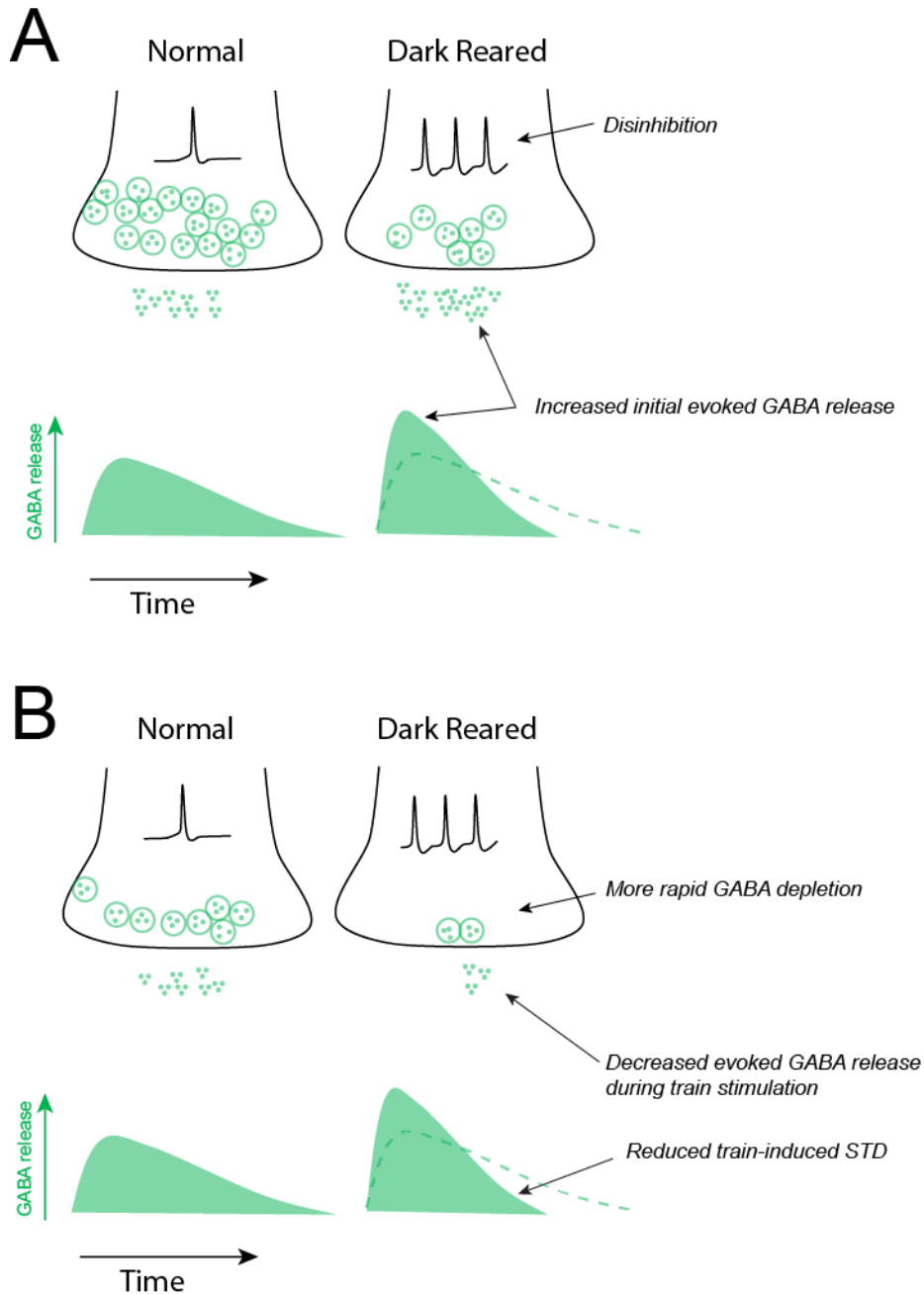


Figure 4.2. Synaptic model of how DR affects GABA release in SC

A) DR causes reduced $GABA_A$ R function, which disinhibits the activity of inhibitory neurons. This disinhibition is represented as 3 spikes instead of one, but DR could increase probability of GABA release without increasing spiking. DR also reduces GABA content in these neurons (Carrasco et al., 2011). The first pulse of a stimulus train causes more GABA release in DR SC than normally reared SC because of the disinhibited inhibitory neurons. The increased GABA release activates $GABA_B$ Rs more

strongly in slices from DR animals, which causes increased PPD compared to slices from normal animals.

B) Longer duration train stimulation, such as occurs during vision, depletes GABA in inhibitory neurons in DR SC more rapidly, because of (1) increased GABA release and (2) reduced GABA content. This causes GABA_BR-mediated STD of excitation to be reduced during longer duration stimulation.

RF enlargement occurs through mechanisms operating on long and short time scales, represented schematically in figure 4.3.

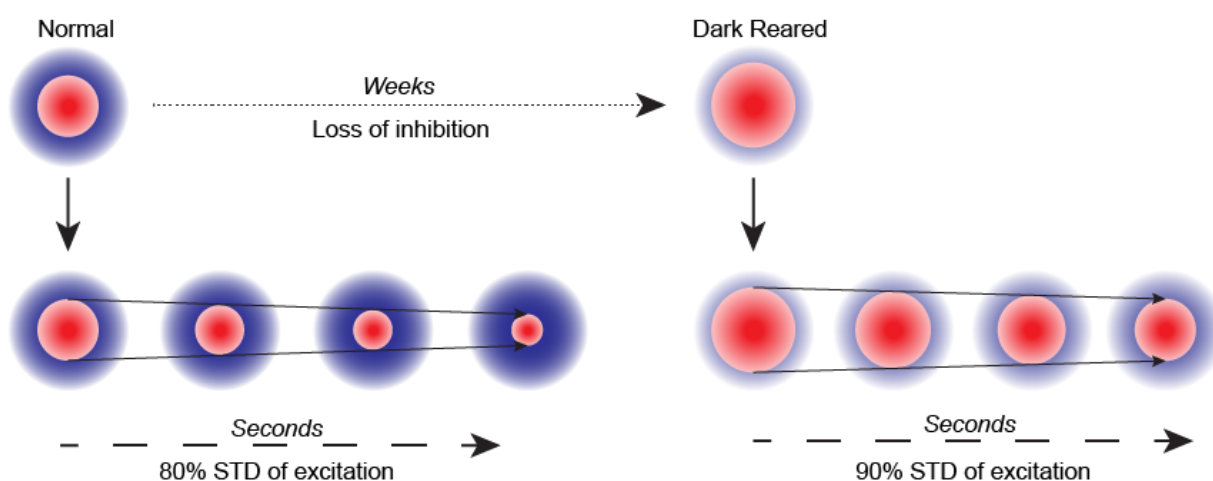


Figure 4.3. DR affects RF by reducing surround inhibition and by reducing short-term depression that occurs during stimulation

In the absence of visual experience, GABAergic inhibition is reduced (Carrasco et al., 2011) and RFs are enlarged in both V1 and SC by P90 (Chapter 2). In Fig 4.3, this is modeled as an increase in the size of the excitatory RF (red) and weaker blue inhibitory surround (blue) and it occurs over weeks. In SC, reduced inhibition further affects RF size on a short time scale because it affects STD (Chapter 3). STD of excitation during the first moments of visual stimulation causes the excitatory RF to shrink. Reduced STD in DR SC causes the RFs to shrink less during visual stimulation. This causes RFs of DR SC to remain larger during stimulation, relative to normal SC.

4.2 Spontaneous activity is sufficient for experience-independent refinement of RFs

In Chapter 2, I showed that spontaneous activity alone is sufficient for RF refinement in both V1 and SC, but that visual experience is necessary to maintain RFs during chronic DR. The finding that V1 RFs refine without visual experience has been corroborated in mice since the publication of Chapter 2, in two independent laboratories (Kang et al., 2013; Sarnaik et al., 2013).

4.2.1 *Is spontaneous activity instructive or permissive for RF refinement in V1?*

As discussed in the introduction, the pattern of spontaneous activity appears to instruct RF refinement in SC (McLaughlin et al., 2003b; Chandrasekaran et al., 2005; Mrsic-Flogel et al., 2005). Is the pattern of spontaneous activity also necessary for experience-independent RF refinement in V1? In contrast to SC, in LGN and V1 the RFs of $\beta 2$ -nAChR knockout mice do refine (Grubb et al., 2003; Grubb and Thompson, 2004; Wang et al., 2009), indicating that mechanisms of RF refinement likely differ between visual areas. Retinal waves mediated by gap junctions and glutamate remain in these mice and may be sufficient for instructing RF refinement in V1. Although retinal waves cease soon after eye opening, spontaneous activity remains at all levels of the visual system. It is possible that the later spontaneous activity that is not carried in waves is essential for RF refinement.

To test whether patterned activity is instructive for RF refinement, NMDARs, which detect a coincident pattern of pre and postsynaptic activity, can be manipulated. One study that reduced NMDAR activity in V1 of ferrets from P21-P50 did not affect stimulus size tuning (Ramoia et al., 2001), which is occasionally used as an indirect measure of RF size in V1. Similarly, V1 RFs refine despite genetic deletion of the NR2A subunit of the NMDAR (Fagiolini et al., 2003), which is the mature form that has a short open time (Flint et al., 1997). However, deletion or blockade of the long open time NR2B subunit that is expressed during RF refinement has not been investigated. Again, in contrast to SC (Huang and Pallas, 2001), NMDAR-dependent coincidence detection (of both spontaneous and visually-evoked activity) appears not to be necessary for RF refinement in V1. Thus, activity is likely permissive, and not instructive, for RF refinement in V1. However, these studies did not separate spontaneous and evoked activity.

To test this hypothesis directly, NMDARs must be disrupted during DR and at the time when RFs are refining (between P30 and P60). DR would block visually-evoked activity completely and NMDAR blockade would disrupt coincidence detection during spontaneous activity, and would identify whether the pattern vs. the quantity of spontaneous activity is necessary for RF refinement in V1. In experiments manipulating NMDARs, care must be taken not to reduce overall activity. Pharmacological blockade of NMDARs has this effect in V1 (Fox et al., 1989; Miller et al., 1989; Fox and Daw, 1993), but not in SC (Cline and Constantine Paton, 1989; Huang and Pallas, 2001). An alternative approach is downregulation of NMDAR expression with antisense oligonucleotides, which reportedly does not reduce overall activity (Roberts et al., 1998; Ramoa et al., 2001).

4.3 What underlies experience-dependent maintenance of RFs?

In Chapter 2, I showed that a brief period of visually-evoked experience is necessary for RF maintenance during chronic DR, in both V1 and SC. This finding has not been corroborated since the publication of Chapter 2. This may be due to the fact that in studies of sensory deprivation, animals are not commonly left in the dark long enough to observe it (~P90, a month after adulthood in Syrian hamsters). It is likely that enlargement of RFs during extended DR has been induced, but was misinterpreted as a lack of developmental refinement, in cases where RFs were not measured at multiple ages.

In Chapter 3, I showed that dysregulation of inhibition causes changes in short-term plasticity (but not long-term plasticity), that could cause RF enlargement by preventing the depression of excitatory responses that occurs during the first moments of visual stimulation. Below I will discuss possible mechanisms of experience-dependent RF maintenance and DR-induced RF enlargement.

4.3.1 *How can 3 days of visual experience prevent DR-induced RF enlargement?*

Previous work in our lab had shown that light from P22-40 was sufficient to prevent DR-induced RF enlargement in SC (Carrasco et al., 2005). In Chapter 2, I extended the work by comparing the

duration of visual experience necessary for RF maintenance in both SC and V1. I found that just 3 days of visual experience from P37-40 was sufficient to maintain RFs during chronic DR in SC, whereas V1 required 7 days (P33-40).

It was surprising that such brief periods of visual experience were sufficient for RF maintenance in SC. The duration of this period should suggest hypotheses about the mechanisms of RF maintenance. In Chapter 3, I investigated changes in GABAR signaling and short-term plasticity that contributes to DR-induced RF enlargement in SC, but the question of how 3 days of light prevents these physiological changes is an open question.

As in SC, in V1 brief periods of light can prevent plasticity that is prolonged by DR. In cats a mere 6 hours of visual experience prevents ocular dominance plasticity that is prolonged by DR (Mower et al., 1983). DR mice have prolonged ocular dominance plasticity as well, but 4 days of visual experience is not sufficient to prevent it (Iwai et al., 2003). The difference in duration of visual experience that is necessary to prevent plasticity between mice and cats could be related to the number of binocular cells, the architecture of the binocular areas of V1, or their sensitivity to monocular deprivation. In cats, almost every neuron in V1 receives some input from both eyes and they are organized in ocular dominance stripes in which neighboring neurons have stronger inputs from the same eye. In mice, only neurons in a small binocular zone have input from both eyes. A shift in ocular dominance may be more easily detected in cats for this reason. In addition, cat V1 responds to monocular deprivation more rapidly than mouse V1 (Gordon and Stryker, 1996), which may indicate that plasticity occurs more rapidly in cats compared to rodents in general.

Just 2 days of visual experience is sufficient to prevent synaptic effects of DR measured in *in vitro*. 2 days of visual experience reduces NMDAR-dependent LTP and LTD (Kirkwood et al., 1996), endocannabinoid-dependent inhibitory (i)LTD (Jiang et al., 2010), and brings IPSC amplitudes down to normal levels in rat V1 (Morales et al., 2002).

Less is known regarding the effect of brief light exposure on plasticity in SC than in V1. The brief period of light that is sufficient to prevent RF enlargement suggests that light might only be required

to *trigger* a process that maintains inhibition, and that the process can continue during DR after the light exposure has ceased. Although these light exposure periods seem brief, a single day of visual experience could produce millions of action potentials and synaptic events that presumably initiate intracellular signaling cascades with lasting consequences. Many changes in excitatory (Lu and Constantine-Paton, 2004) and inhibitory (Shi et al., 1997) neurotransmission occur during the first day after eye opening. Rapid insertion of GABA_ARs can occur during stimulation (Nusser et al., 1998), which would be caused by light exposure. Indeed, once the process of experience-dependent proliferation of GABAergic synapses is triggered, it is not arrested by DR (Chattopadhyaya et al., 2004). The hypothesis that visual experience triggers the expression of a BDNF-regulating transcription factor that underlies maintenance of RFs is described below.

4.3.1.1 What molecular mechanism could be triggered by 3 days of visual experience and cause RF maintenance?

Visual experience could trigger gene transcription that leads to maintenance of RFs. For example, visually-evoked activity in visual cortical neurons causes an increase in BDNF expression, which increases TrkB phosphorylation and strengthens inhibition (Rutherford et al., 1997; Huang et al., 1999). Npas4 is a transcription factor that is expressed during visual activity, activates the transcription of BDNF (Lin et al., 2008) and may be one of the early visual experience-dependent signals that mediates RF maintenance.

In preliminary work, I showed that exposing DR hamsters to light causes a marked increase in Npas4 expression in both SC and V1 compared to littermates (Fig. 4.4).

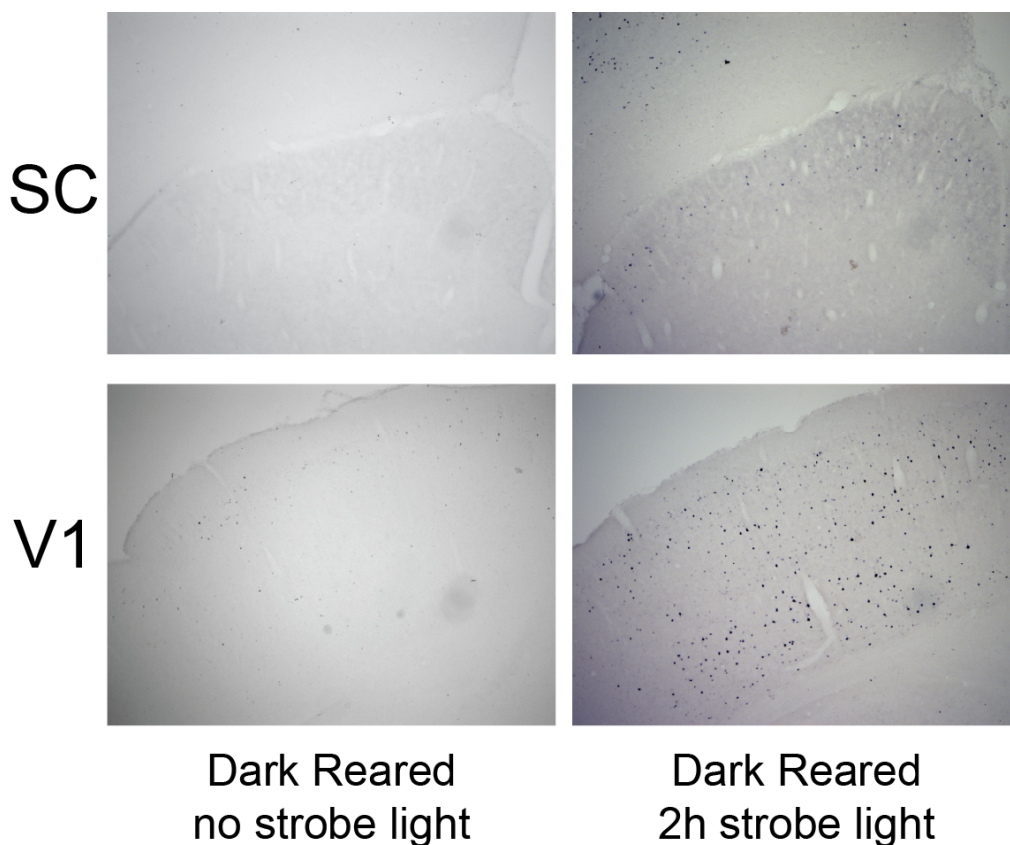


Figure 4.4. Brief visual experience increases Npas4 immunoreactivity in SC and V1.

Future work in could test whether visual activity-dependent Npas4 expression increases BDNF expression and TrkB phosphorylation, thus triggering the stabilization of GABAergic inhibition and preventing RF enlargement in DR SC.

The first experiment proposed was a test of whether visual experience-dependent TrkB signaling prevents DR-induced RF plasticity. Can exogenous TrkB activation replace visual activity from P37-40 and prevent the RFs of DR animals from enlarging by P90? I predicted that increasing TrkB signaling in DR animals from P37-40 with a TrkB agonist (7,8-dihydroxyflavone, 10 mg/kg IP, once per day (Jang et al., 2010)) would prevent RF enlargement after P90, compared to vehicle-injected control littermates.

Systemic injections of this TrkB agonist has been reported to increase TrkB phosphorylation in hippocampus (Devi and Ohno, 2012). In our hands, however, we have not been able to show that systemic injection of the TrkB agonist increases TrkB phosphorylation in SC and V1. These studies are ongoing in the Pallas lab.

4.3.2 *Is visual experience permissive or instructive for RF maintenance?*

Our studies have shown that visual experience is necessary for RF maintenance, but we have not identified whether visual experience plays a permissive or instructive role. If visual experience is permissive, then the pattern of activity does not matter. It would be possible to test the hypothesis that visual experience is permissive for RF maintenance by providing retinocollicular activity exogenously from P37-40. This could be done in several ways.

An implanted electrode in the SC or optic nerve could provide stimulation with a different pattern than occurs with visual activity. A simpler manipulation would be to change the visual environment. A strobe light could be used to provide visual stimulation without the coherent pattern provided by normal visual experience. One study showed that 6-8 month old hamsters reared from birth under strobe light had normal RF sizes in SC, which suggests a permissive role of visual experience (Chalupa and Rhoades, 1978b). However, in the same study, size tuning was slightly less selective (Chalupa and Rhoades, 1978b), indicating the possibility that inhibition was reduced (Razak and Pallas, 2006). If inhibition was reduced by chronic strobe rearing, it may have occurred through a failure to develop or a failure to maintain inhibition. Future work is necessary to clarify whether visual experience provides a pattern that is instructive, or a level or stimulation that is permissive, for maintenance of RF properties and GABAergic inhibition.

4.3.3 *Could other forms of plasticity contribute to DR-induced RF enlargement?*

In Chapter 3, I investigated long and short-term synaptic plasticity. Other forms of plasticity, including homeostatic synaptic plasticity and non-synaptic intrinsic plasticity, also exist and could contribute to RF plasticity (Mozzachiodi and Byrne, 2010).

Homeostatic synaptic plasticity occurs when the input activity of a neuron is reduced or increased and synaptic efficacy changes inversely, in order to keep activity at a set point (Turrigiano and Nelson, 2004). Synaptic scaling is one form of homeostatic plasticity and can occur through increases in

postsynaptic excitatory receptors, increases in vesicle content, or increases in vesicle release probability (Rich and Wenner, 2007).

It is certainly possible that mechanisms of homeostatic synaptic plasticity contribute to DR-induced RF enlargement, especially in V1, because increased excitatory synaptic strength would likely increase spontaneous activity. DR causes an increase in spontaneous activity in V1 (Cf. Fig. 2.6), but does not affect spontaneous activity in SC (Carrasco et al., 2005), which argues against this hypothesis.

DR for two days at any age causes scaling up of quantal amplitude in mouse V1, which is reversed by one more day of light exposure thereafter (Goel and Lee, 2007). This indicates that V1 scales quantal amplitude up and down rapidly in response to the level of visual experience, and this likely occurs in DR hamsters. However, it also suggests that synaptic scaling is not likely to be a major contributor to DR-induced RF enlargement in my experiments, because DR does not affect RF size when RFs have already expanded (Carrasco and Pallas, 2006), although it would likely affect quantal amplitude. Synaptic scaling may contribute to the maintenance of peak response or spontaneous activity levels.

Intrinsic plasticity is a change in the output of a neuron despite the same synaptic input, which is caused by a change in the neuron's intrinsic electrical properties (Daoudal and Debanne, 2003; Desai, 2003; Zhang and Linden, 2003; Mozzachiodi and Byrne, 2010; Wenner, 2014). Changes in input resistance, spike threshold, or ionic conductances can alter intrinsic excitability (Turrigiano et al., 1994; Desai et al., 1999; Cudmore and Turrigiano, 2004). Such changes generally occur with development, but can occur for other reasons as well. For example, increased input resistance of a neuron could increase the depolarizations caused by excitatory synapses. Ohm's law states that $V = I * R$. If the resistance of the cell (R) increases and the synaptic current (I) is constant, the voltage output (V , membrane depolarization) will increase. DR, however, affects neither the input resistance nor the resting membrane potential of V1 neurons (Desai et al., 2002; Morales et al., 2002). Similarly, sensory deprivation has no effect on the intrinsic excitability of somatosensory cortical neurons (Cheetham and Fox, 2011). Thus, it is unlikely that changes in intrinsic excitability contribute to RF enlargement in V1.

Few studies have addressed homeostatic synaptic plasticity or intrinsic plasticity in SC. There is evidence that visual activity causes synaptic scaling in goldfish tectum (Riegle and Meyer, 2007) and intrinsic plasticity in *Xenopus* tadpole (Aizenman et al., 2003; Pratt and Aizenman, 2007). Although the RFs of SC neurons in $\beta 2$ -nAChR knockout mice fail to refine, intrinsic excitability is unaffected (Shah and Crair, 2008), indicating that intrinsic excitability is separable from RF size in SC. In sum, there is no evidence that intrinsic plasticity underlies RF plasticity in SC, although future studies are necessary to test this hypothesis directly.

4.3.4 Visual experience-dependent changes in STD could affect sensory processing in SC

DR causes reduced GABAergic inhibition and increased probability of glutamate release, both of which could increase sensitivity to light. This could be an advantage to an animal born into a dark environment or with visual pathologies that could cause reduced vision such as cataract. However, there are several apparent tradeoffs for this increased sensitivity to light.

STD in SC is thought to underlie novel stimulus detection (Platt and Withington, 1997). Visual responses that occur at the same place in the visual field and retina are ignored because they activate the SC less and are therefore less likely to cause a motor output to orient to the stimulus. In this case, DR animals may have difficulty identifying novel stimuli, beyond the issues associated with low visual acuity alone.

In addition, STD acts as a temporal filter- it reduces the influence of fast spiking inputs on a neuron and increases the sensitivity to slower spiking inputs (Fortune and Rose, 2001). Thus, STD is a mechanism of gain control (Abbott et al., 1997) and network stability (Galarreta and Hestrin, 1998). Reduced STD in SC could disrupt temporal filtering and may prevent stimuli that evoke slow spiking from being perceived, because they are obscured by the fast spiking inputs that do not depress enough to reveal them. Direction tuning could be affected, because it is mediated by STD in V1 (Chance et al., 1998) and in midbrain of weakly electric fish (Chacron et al., 2009).

V1 RFs are known to change size depending on stimulation (Pettet and Gilbert, 1992; Zhu and Yao, 2013). For example, high contrast stimuli reveal smaller excitatory RFs than low contrast stimuli presented to the same neuron (Sceniak et al., 1999; Chen et al., 2013). We reason that STD may underlie this phenomenon. When presented with high-contrast stimuli, V1 neurons respond maximally, likely resulting in more STD than when presented with low-contrast stimuli that elicits a less than maximal response. This notion, combined with our model that suggests STD causes RFs to shrink during visual stimulation, indicates that high contrast stimuli could elicit smaller RFs than low contrast stimuli, because of the different magnitudes of STD that they cause. DR may be an experimental paradigm that could be used to test the role of STD in these properties of sensory processing.

4.4 Critical periods in visual circuits

Critical periods for different visual properties coexist and overlap in the same brain area and in the same neurons (Daw and Wyatt, 1976; Jiang et al., 2007; Huberman et al., 2008). For example, the critical period for direction selectivity in cat V1 occurs weeks before the critical period for ocular dominance plasticity (Blakemore and Van Sluyters, 1974; Daw and Wyatt, 1976; Berman and Daw, 1977). The critical period for homeostatic synaptic scaling occurs before the critical periods for both direction and ocular dominance (Desai et al., 2002).

In addition, there are different critical periods for development, plasticity and recovery of the same RF property. For example, ocular dominance columns develop by P20 in ferrets, remain plastic and sensitive to experience until P60 (Crowley and Katz, 2000), and reverse occlusion allows recovery from monocular deprivation much later (Liao et al., 2004).

The meaning of the term critical period has changed since it was first used by Hubel and Wiesel (1963) to describe the time during which visual experience is essential for normal development, to a time when a circuit is especially plastic. In general, it seems that as experiments provide more detail about the phenomenon, most critical periods are less circumscribed than first reported.

The timing of critical periods can depend on the techniques used to assess them. Immediate early gene transcription shows robust ocular dominance plasticity longer than does electrophysiological assessment (Pham et al., 2004; Tagawa et al., 2005). *In vivo* extracellular visually evoked potential (VEP) recordings, which measure a summed synaptic potential produced by the synchronous activity of many neurons, also reveal long critical period duration (Sawtell et al., 2003), in contrast to *in vivo* single unit recordings (Gordon and Stryker, 1996), likely because they sample different activities. The anesthetic used for *in vivo* measurement of ocular dominance is also crucial. Ocular dominance plasticity appears to occur in adults if measured with VEPs under urethane anesthesia, but is occluded by barbiturate anesthesia in the same animals (Pham et al., 2004).

4.4.1 Is experience-dependent RF maintenance subject to a critical period?

As discussed above, the term critical period can quickly become a misnomer as data accumulate. This inevitability may be reason enough to refrain from referring to the experience-dependent prevention of RF plasticity as having a critical period. Moreover, it is somewhat difficult to relate the pattern of RF refinement and maintenance to the canonical critical period of ocular dominance plasticity, in which monocular deprivation causes a more complete ocular dominance shift during the critical period than before or after. In our model of RF plasticity, visual experience prevents RF enlargement from occurring *in the future*. The critical period for prevention of RF enlargement is anywhere from P22-90 in SC and P22-40 or later for V1 (the effect of light after P40 has not been tested), and only requires a few days of visual experience.

Experience-dependent prevention of RF plasticity may be better described as metaplasticity. Metaplasticity is a change in the ability to undergo plasticity or in the amount of plasticity that occurs (Abraham and Bear, 1996; Abraham, 2008). For example, in metaplasticity, a priming event allows later stimuli to cause a different amount of plasticity than would have occurred before the priming event. Visual experience prevents DR-induced RF enlargement. Thus, visual experience is the priming event

that prevents plasticity during later chronic DR. Visual experience decreases metaplasticity of RF size and DR increases metaplasticity of RF size.

4.4.2 Critical periods differ between brain areas

Visual deprivation appears to have a larger effect on higher levels of the retinogeniculocortical visual pathway than on lower levels. This makes logical sense, given that higher levels require consistent and precise input from lower levels in order to function properly. The retina is affected even less by visual deprivation (Sherman and Stone, 1973; Cleland et al., 1980; He et al., 2011; Akimov and Renteria, 2014) and activity blockade (Sun et al., 2011; Wei et al., 2011). Retinal responses measured by electroretinogram are not affected by deprivation (Reuter, 1976), nor is the development of direction or velocity tuning in RGCs (Chan and Chiao, 2008; Elstrott et al., 2008), although anatomical segregation of ON and OFF pathways is disrupted, resulting in more RGCs that respond to both stimulus onset and offset (Tian and Copenhagen, 2003). Monocular deprivation causes the cell bodies of LGN neurons innervated by the deprived eye to shrink physically (Wiesel and Hubel, 1963) and reduces visually evoked potentials, but does not affect spatial resolution (Shapley and So, 1980).

Visual deprivation affects V1 much more profoundly than it affects retina and LGN. The observation that plasticity occurs earlier in the lower levels of the visual system holds for different layers within V1. The critical period for ocular dominance plasticity occurs earlier in layer 4 (the input layer) than in layer 2/3 (Hubel and Wiesel, 1970; Daw et al., 1992) as does the critical period for monocular deprivation-induced synaptic scaling (Desai et al., 2002). Layers within somatosensory cortex (Fox, 1992) also follow the pattern of areas farther from the sense organ having a later critical period onset. Postnatal maturation of visual areas also appear to occur earlier in lower visual areas (Condé et al., 1996; Guillery, 2005).

The reason that higher visual areas are more affected by visual deprivation is likely due to the importance of experience-dependent plasticity to their function in perception. Visual areas receiving V1 input likely maintain some plasticity indefinitely, because they are responsible for face recognition and

memory, which is clearly flexible throughout life (Squire et al., 2004; Hübener and Bonhoeffer, 2010). In contrast to higher visual perceptual properties, detection of luminance, stimulus onset and offset, movement, edges, orientations, and depth, is unlikely to require flexibility in adulthood. Under normal circumstances, restricting plasticity in primary sensory areas after refinement has occurred could be advantageous, because it prevents regression to an immature or unrefined state, as can occur in disease (Durand et al., 2012).

4.4.3 Critical periods differ between species

It is unclear why development of the same physiological property takes relatively longer in some species than others. The duration of critical periods appears to correlate with lifespan (Berardi et al., 2000). However, this ignores innumerable confounds. The animals used for the correlation included only rats, mice, ferrets, cats, monkeys and humans. Indeed, it is likely that gestational length, time of eye opening, body size, brain size, and orbit size would also correlate with critical period duration in this sample. It would be interesting to investigate whether critical period duration correlates better with brain size, neuron number (Charvet et al., 2013), neuron/glia ratio, synapse complexity, or simply developmental pace (Clancy et al., 2001).

In order to elucidate why critical period duration differs between species, more varied species must be studied. The order Rodentia is remarkably diverse in visual capacities and represent an opportunity for comparative study (Finlay et al., 1980). In particular, species with similar lifespans but different visual capacities and sizes could reveal mechanisms that control critical period duration. In addition to hamsters, rats, and mice (*Myomorpha* suborder), which have relatively poor vision and are small, species in other rodent suborders may be of interest. Squirrels (*Sciuromorpha*) have good vision and are medium sized. Capybara and paca (*Hystricomorpha*) also have good vision and are among the largest rodents (Wilson and Reeder, 2005). Comparing critical period duration across these species would help identify parameters that relate to critical period plasticity.

4.5 RF refinement and plasticity as a substrate for evolutionary change

A useful way to think about evolution is to compare the role of the genome to the role of experience in the development of an organism's phenotype. In addition to the necessary role of the genome, experience clearly shapes the phenotype of an organism. This is referred to as phenotypic plasticity- the variation of a phenotype caused by the environment (West-Eberhard, 2003; Pfennig et al., 2010). As described above, DR-induced RF enlargement could increase sensitivity to light in a dark environment. The capacity for experience-dependent plasticity could provide an advantage to an animal and could therefore be subject to selection pressure.

Age-dependent phenotypic plasticity is more likely to exist when an organism does not have good information about the environment before or at birth (Fischer et al., 2014). Perhaps RFs refine by default in hamsters because they live underground and may not see light until weeks after birth. If the organism has no information about the environment it will live in (outside the burrow) it could be advantageous to assume that high acuity is necessary and that there will be sufficient light. RF plasticity in adulthood could provide an organism a way to fine-tune its visual system to an unpredictable postnatal environment. If the assumption of sufficient light after leaving the burrow was incorrect, and the organism must live in a low-light environment, RFs of Syrian hamsters are able to expand.

There are also costs associated with experience-dependent plasticity: irreversibility, for example. If an animal develops in a dark environment and the RFs are enlarged in order to adapt to low light conditions, but then it moves to a brighter environment, the visual system will not match the new surroundings. If the animal had had experience-independent refinement and no further DR-induced plasticity, it would be better off when moved to a lighter environment in adulthood. If experience-dependent plasticity has been selected for, then presumably the benefits to fitness outweigh the costs.

Alternatively, it is possible that experience-dependent plasticity has been selected for, not because of an advantage provided by phenotypic plasticity, but rather, because it is an effective way to build the nervous system. The genome is finite and does not have the capacity to specify the complex wiring of the brain. Instead, it contains rules that axons follow during synaptogenesis and pruning.

It is also possible that experience-dependent plasticity is an exaptation, not directly selected upon, but genetically linked to some other process that provides a reproductive advantage. For example, the same genes that allow experience-dependent plasticity may be linked to another process in which experience is required for survival.

The interaction between the endocrine system and the environment has been proposed to induce phenotypic plasticity (Ketterson et al., 1996; Dufty et al., 2002). Hormones could be important to study in the context of plasticity, because critical periods typically end around puberty. Cortisol reduces the amount of ocular dominance plasticity that occurs during the critical period (Daw et al., 1991), but testosterone does not (Daw et al., 1987). DR may lead to a chronic increase in melatonin, because melatonin increases in the dark (Reiter, 1991). Interestingly, systemic administration of melatonin reduces cortical LTP *in vivo* (Soto-Moyano et al., 2006) and there is evidence that DR reduces this sensitivity to melatonin in acute hippocampal slices (Talaie et al., 2010). More studies are required to address whether hormone levels around puberty contribute to the expression of visual plasticity.

4.6 Clinical implications

4.6.1 Recovery from deprivation after the critical period in visual systems?

Until recently, the notion that normal visual experience is necessary to develop vision was assumed to be true for humans. A group of scientists is changing this perspective by treating adolescents and teenagers that have had bilateral cataracts since birth. They have found that, after cataract removal, many patients develop markedly improved contrast sensitivity (Ostrovsky et al., 2006; Kalia et al., 2014). Visual acuity in adults with amblyopia can also be improved by playing video games (Li et al., 2011; Hess et al., 2012; Jeon et al., 2012). Thus, in humans, plasticity allows recovery from visual deprivation much later than previously appreciated.

The studies described in Chapter 2 and 3 also suggest that plasticity can occur in adulthood and can be initiated by visual deprivation. In addition to behavioral therapies (Hunter, 2005; Hess et al.,

2010), visual deprivation has been proposed as a potential application to promote recovery of visual function (Duffy and Mitchell, 2013; Mitchell and Duffy, 2014).

4.6.2 Critical periods in human learning

Some humans possess absolute pitch- the ability to identify the pitch of a sound without any reference point. Development of absolute pitch is rare and requires practice during a critical period (Takeuchi and Hulse, 1993). A recent study showed that human adults given valproate, a histone-deacetylase inhibitor, were able to learn absolute pitch after the critical period (Gervain et al., 2013). This remarkable finding suggests that critical periods can be reopened in adult humans. It is unclear whether the effect of valproate was due to an epigenetic mechanism, but it is possible, because epigenetic changes appear to be one of the many factors that control ocular dominance plasticity (Putignano et al., 2007). Learning absolute pitch relates to language development. Speakers of languages that modulate pitch, such as Mandarin, have an advantage in learning absolute pitch (Deutsch et al., 2006). It is possible that treatments that help adults learn absolute pitch could also help in language learning.

4.6.3 Clinical implications related to plasticity of GABAergic inhibition

Sensory deprivation occurs in humans with diseases that occlude or disrupt retinal processing, including macular degeneration and cataract (Lewis and Maurer, 2009) and reduces inhibition in visual circuits. Moreover, given the important role of inhibition in neural processing across the brain, it is likely that changes in inhibition contribute to many disorders beyond those caused by sensory deprivation.

Dysregulation of inhibition disrupts sensory processing by affecting surround suppression, stimulus selectivity, and by allowing changes in short-term plasticity that would not occur under normal conditions. Inhibitory surround suppression affects perception in humans and can be measured in visual tasks (Tadin et al., 2003). Perceptual testing in humans suggests that surround suppression is reduced by aging (Betts et al., 2005), depression (Golomb et al., 2009) and schizophrenia (Tadin et al., 2006).

Understanding the development and plasticity of GABAergic inhibition could relate to these disorders (Takesian and Hensch, 2013).

4.6.4 Clinical implications related to short-term plasticity

Short-term plasticity occurs at virtually all synapses in the brain and any disruption can lead to serious impairment in function (Abbott and Regehr, 2004). Short-term plasticity is affected by neurodegenerative or psychiatric disorders (Arguello and Gogos, 2012) and by factors such as brain injury (Li et al., 2005), seizures (Hernan et al., 2013), or deafness (Takesian et al., 2010). Identifying how short-term plasticity is regulated in general and how it is affected by the environment could provide new avenues to study the etiology and treatment of pervasive neurologic and psychiatric disorders.

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