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MECHANISMS UNDERLYING MAINTENANCE OF ADULT VISUAL RECEPTIVE
FIELDS

by

DAVID B. MUDD

Under the Direction of Sarah L. Pallas Ph.D

ABSTRACT

The establishment of neuronal connections requires a sequence of orchestrated events including neuronal migration, axon guidance, synapse formation and elimination, and circuit fine-tuning. Understanding the molecular signaling pathways that underlie these processes is fundamental to understanding how the nervous system is assembled and how it functions. In this dissertation, I investigated the molecular mechanisms mediating the effects of visual experience in the development and plasticity of the visual pathway. Each neuron receiving visual input responds to a specific area of the visual field- their receptive field (RF). During early development RFs refine in size, an important property of visual acuity. Utilizing the sensory deprivation model of dark rearing (DR) in Syrian hamsters (*Mesocricetus auratus*), I

investigated the signaling mechanisms underlying RF refinement and plasticity. Our lab has previously reported that the developmental refinement of RFs happens independently of visual experience in both superior colliculus (SC) and visual cortex (V1), but fails to be maintained without sufficient visual experience during an early critical period (CP). Using a pharmacological approach, I show that BDNF/TrkB signaling is crucial for the maintenance of RF refinement in SC. DR hamsters treated with a TrkB agonist during the CP for RF refinement maintenance (P33-P40) have mature RFs in adulthood. Hamsters given visual experience, but treated with a TrkB antagonist during the CP have enlarged (unrefined) RFs in adulthood. I also show that refined RFs are essential for enhancing both looming escape behaviors, and spatial discrimination of sinusoidal gratings. How early visual experience prevents plasticity in adulthood (resulting in a loss of RF maintenance) is poorly understood, but reduced GABAergic inhibition is involved. Using a molecular approach I identified several possible mechanisms mediating a loss of inhibition in SC of DR adults. Ultimately it appears that reduced expression of the GABA neurotransmitter is primarily responsible for loss of RF maintenance, rather than any post synaptic modifications. This work provides insight into the mechanisms of development and plasticity in the nervous system and could instruct therapies to prevent maladaptive plasticity in disease and to enhance recovery of function in adults.

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

MECHANISMS UNDERLYING MAINTENANCE OF ADULT VISUAL RECEPTIVE
FIELDS

by

David B. Mudd

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy

in the College of Arts and Sciences

Georgia State University

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David Brian Mudd
2019

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by

DAVID B. MUDD

Committee Chair: Sarah L. Pallas

Committee: Daniel Cox

Angela Mabb

Peter Wenner

Electronic Version Approved:

Office of Graduate Studies

College of Arts and Sciences

Georgia State University

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DEDICATION

I am grateful for the support of my family, friends, and in particular my loving wife Lauren for supporting me through late nights of work and long hours of writing and editing. I am also thankful for my two dogs that always provide social and emotional support from the moment I get home until the moment I leave in the morning.

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LIST OF ABBREVIATIONS

ALS – amyotrophic lateral sclerosis
AMPA – α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor(s)
BDNF – Brain derived neurotrophic factor
CNS – Central nervous system
dLGN – dorsal lateral geniculate nucleus
GABA – gamma(γ)-aminobutyric acid
GABAARs – gamma(γ)-aminobutyric acid receptors
HAP1 – Huntingtin associated protein 1
LGN – Lateral geniculate nucleus
LTD – Long-term depression
LTP – Long-term potentiation
nAChR – nicotinic acetylcholine receptor
NGF – Neural growth factor
NMDAR – N-methyl-D-aspartate receptor(s)
NT-3/4 – Neurotrophin 3 or 4
ODC – Ocular dominance columns
ODP – Ocular dominance plasticity
POR – Post rhinal cortex
RF – Receptive field
RGCs – Retinal ganglion cell(s)
SC – Superior colliculus
SGS – superficial gray layer (of superior colliculus)
TrkA/B/C – Tropomyosin receptor kinase A or B or C
TTX – Tetrodotoxin
V1 – Primary visual cortex

1 INTRODUCTION

Our experiences in life depend on the ability of our nervous system to provide us with a sense of the world around us. As the nervous system grows and matures, we gain sensitivity to new stimuli in the environment along with the ability to process these stimuli in new ways. Intriguingly, this enhanced sensitivity is due in part to the environment exerting influence on the nervous system's own development. Sensory experiences allow the nervous system to adapt itself in order to optimally respond to features present within the environment. However, after a certain time point in development, much of this flexibility is lost and adaptations require more effort or are no longer possible.

These early windows in time where environmental experiences can shape the nervous system are called critical periods. During development, critical periods facilitate the functional or structural maturation of neural systems (Hensch, 2004; Malik et al., 2013). Once critical periods close, circuits stabilize and are prevented from returning to an immature state. Often modality specific experiences during the critical periods are necessary for this stabilization to occur. For example, neurons in primary visual cortex (V1) in cats are sensitive to the direction of motion of visual stimuli, but cats reared under a strobe light and thus deprived of motion stimuli, fail to develop this sensitivity (Cynader et al., 1973).

Although sensory experience is clearly an important contributor to critical period regulation, the overall role of sensory experience in shaping neural circuits remains a major question in developmental neuroscience. One commonly held interpretation of existing data is that normal circuit development requires modality specific input during critical periods, without which the circuit fails to form at all. Another possibility is that sensory circuits form independent of sensory instruction, but experience during the critical period reinforces and

maintains those circuits throughout life. The goal of this introduction is to provide a context for how these alternatives have been examined thus far, why the study of experience-dependent development is critical to our understanding of the brain, and to provide a background for the research presented in Chapters 2 and 3.

1.1 The visual nervous system

Due to the relative ease of controlling an organism's environmental experiences, sensory systems are popular for studying experience-dependent development. The visual system is especially useful because it receives both spontaneously generated and sensory-evoked (visual) neural activity. It has been extensively studied over the last seventy years because visual activity can be manipulated by surgical, pharmacological, and rearing environment interventions. In this section I review current data on the anatomical and functional development of the visual system, on the contributions of spontaneous and evoked activity, and on what is known about the regulation of critical periods in mammalian visual systems. I then synthesize the state of knowledge and propose possible mechanisms that could account for visually driven circuit development.

1.1.1 Retinal circuits and cell types

The transduction of visual stimuli into the electrical currency of the nervous system begins within the retina, a stratified network of cells. Photoreception occurs in the rods and cones in the outermost layer of the retina. Rods function best in low-light conditions and vastly outnumber the cones (20 to 1) in most mammalian organisms (Curcio et al., 1990), although cones, which are located in the center of the retina (fovea or visual streak), are responsible for

high visual acuity and color perception. After light is transduced to a chemical signal by the photoreceptors, the information is converted into electrical signals and filtered through a series of interneurons (bipolar, horizontal, and amacrine cells) in the adjacent layers of the retina. The filtered signals are then transmitted to the retinal ganglion cells (RGCs) at the innermost layer of the retina. The RGCs are the only centrally-projecting neurons in the retina and their axons form the optic nerve, which carries visual information to the brain. There are currently over 30 different known types of RGCs, each optimally responding to a different aspect of visual stimuli (Baden et al., 2016). (For a comprehensive review of different RGCs and their relative contributions to visual processing see Masland, 2001; Dhande and Huberman, 2014; Dhande et al., 2015; Sanes and Masland, 2015; Rheaume et al., 2018).

1.1.2 Visual brain areas, ocular dominance, and retinotopic mapping

The optic nerve decussates at the optic chiasm, after which it is referred to as the optic tract. Information from each eye projects almost exclusively to the contralateral side of the brain in rodents, but in carnivores and primates, the tracts carry both ipsi- and contralateral RGC axons, thus each eye innervates both sides of the brain to varying extents. These axons innervate many brain structures including the lateral geniculate nucleus (LGN) of the thalamus and the superior colliculus (SC) of the dorsal midbrain, two areas that have specialized functions, and influence cortical responses differently (Schneider, 1969; Stein et al., 2016; Ito and Feldheim, 2018).

1.1.2.1 Lateral geniculate nucleus

The dorsal LGN functions as the principal relay for sending retinal information to the cortex, where higher visual processing takes place (Grubb et al., 2003). However, the retina only accounts for a small percentage of total LGN input, with approximately 95% coming from V1, SC, thalamic reticular nuclei, pretectum, and local interneurons (Guillery and Sherman, 2002). These inputs provide secondary processing (clarifying and enhancing visual feature discrimination) feedforward, and feedback signaling. RGCs from the contralateral eye innervate the majority of the territory in dLGN of mammals with minimal binocular overlap, including rodents. In carnivores and primates, ipsilateral and contralateral RGCs are segregated into different laminae within dLGN (Muir-Robinson et al., 2002; Huberman et al., 2003; Jaubert-Miazza et al., 2005; Howarth et al., 2014). The LGN is divided into six layers (1-6) in humans and non-human primates, with the ventral 2 comprising the magnocellular (M) layers, and the dorsal 4 parvocellular (P) layers. Between each P/M layer are additional types of neurons that make up the koniocellular layers. The outgoing axons from LGN fan out and travel through the internal capsule, with the majority ultimately terminating in V1 (Hubel and Wiesel, 1972; Henderickson et al., 1978).

1.1.2.2 Primary visual cortex (V1)

Primary visual cortex, also known as area 17, striate cortex, or V1, is the first cortical area to receive visual input and is perhaps the visual area of the brain that is most studied by developmental neuroscientists. This may be because V1 houses the brain circuits that allow for binocular vision. Most of the axons from dLGN innervate layer 4. It is within layer 4 that ocular dominance columns (ODCs) - a cortical feature discovered in classic studies of cat and primate

V1 (Hubel and Wiesel, 1962, 1969) - can be most readily observed. These ODCs can be described as alternating stripes of right or left eye dominated cortical territories in most primates, but in many carnivores and rodents they are better described as patchy, and in mice they fail to form at all (Drager, 1975).

From layer 4 (also called the granular layer due to its small cells) axons project to layers 2 and 3, which send signals horizontally within and between cortical areas. Layer 2/3 neurons receive convergent input from both eyes, and are thus the first point of binocularity in the visual pathway. Changes in binocularity and ODCs have been extensively examined in studies of ocular dominance plasticity (ODP). These studies attempt to explain how early sensory deprivation can exert a persistent and devastating effect on visual function (Jacobson et al., 1981). Although the mechanisms underlying ODP are not directly examined in this dissertation, the concepts revealed from work studying the critical period of ODP have been quite influential (see Hensch, 2005b for review).

Axons from layer 2/3 (supergranular layers) also send signals to layers 5 and 6, which in turn form several excitatory projections extending outside of V1. Layer 6 provides feedback to LGN, and layer 5 projects to SC and other subcortical targets. V1 also projects to several other cortical areas for higher processing (Marshall et al., 2011; Garrett et al., 2014), which in turn often project back into and feed processed information back into V1 (Felleman and Van Essen, 1991). Although the underlying structure of V1 has been extensively studied, much remains to be learned about the mechanisms governing the development of the intracortical and extrastriate connections outlined in this section.

1.1.2.3 Superior colliculus

The retina also projects directly to the SC, also known as the optic tectum in non-mammalian vertebrates. The SC is a multimodal sensorimotor midbrain area that orients the head and eyes toward stimulus locations in the environment (Mort et al., 1980; Isa, 2002) but also receives auditory and somatosensory input (Stein and Arigbede, 1972; Gharaei et al., 2018). The optic tract enters the stratum opticum layer of anterior SC and retinal terminals innervate neurons in the superficial gray layer (SGS), in which the cells process visual stimuli exclusively. Much like in dLGN, ipsilateral projections from the retina are segregated in anterior SC but contralateral projections project throughout SC (Dräger and Olsen, 1980; Godement et al., 1984). The SC also receives corticocollicular projection from layer 5 of V1 (Rhoades and Chalupa, 1978), whereas the more ventral layers of SC receive input from other sensory modalities and deep layers provide motor commands.

One interesting characteristic of the SC is how variable the architecture and functions are between different species. For example, in mice ~90% of RGCs project to the SC (Ellis et al., 2016), a stark contrast to the ~10% of RGCs that project to SC in primates (Perry and Cowey, 1984). Indeed, the proportional size of SC can vary greatly between species. In primates, the massive expansion of the cerebral cortex is associated with a reduction in the relative size of the SC (as a percentage of the entire brain), and a reduction in overall importance because many aspects of visual processing are taken over by cortex (Northcutt, 2002). In non-mammalian vertebrates, which do not have a cerebral cortex, the tectum (SC) is one of the largest structures in the brain, and is responsible for a great deal of the visual, auditory, and somatosensory processing. For example, in snakes, nearby infrared radiation is transduced via the trigeminal

nerve, but is then processed like other parts of the visual pathway in the optic tectum (Naumann et al., 2015).

1.1.2.4 Retinotopic mapping

In mammalian species LGN, SC, and V1 contain a topographic representation of the retinal surface, also known as a retinotopic map (Wang and Burkhalter, 2007; Garrett et al., 2014). Retinotopic maps arise from the spatial pattern of RGC projections to their targets, and visual acuity is related to the degree of axonal convergence that the innervating axons have on the post synaptic neurons. Retinotopic maps are aligned across the various layers of LGN and V1, as are the connections between them.

Retinotopic maps begin to form early in postnatal development, and are initially directed by axon guidance factors and then refined by patterned spontaneous activity. The mapping of the RGCs onto the brain is instructed at least in large part by the chemorepulsive signaling of the ephrin system. The EphA receptors for ephrinAs, located on the RGC growth cones, are repulsed by the ephrin A ligand gradient expressed throughout SC and dLGN (Henkemeyer et al., 1996; Brückner et al., 1997; Wang et al., 1999). Eliminating ephrinA ligands in early development has been shown to disrupt retinotopic map formation along the azimuthal axis in mammals (Feldheim et al., 1998; Cang et al., 2005a; Pfeiffenberger et al., 2006; Cang et al., 2008). EphrinBs are implicated in the mapping of the elevation axis of the retina, though their role appears to be more complex than for ephrinAs. For example, Wnt/Ryk signaling has been shown to either complement or replace ephrinBs in mapping the medial-lateral axis of retinotectal maps in mice (Schmitt et al., 2006). Although the role of the ephrin system in

retinotopic mapping has been widely studied, much work remains to be done about which ephrins are essential and which are supportive in the process.

Neural activity has also been shown to play an active role in retinotopic map refinement (Leary et al., 1986; Cline and Constantine-Paton, 1989). Surprisingly, RF refinement is underway before most mammals can open their eyes (and before photoreceptors are fully wired into the retina), suggesting that this activity is not coming from visual sensory experience, but rather is spontaneously generated (Galli and Maffei, 1988; Meister et al., 1991). Retinal waves (initially generated by spontaneous nicotinic cholinergic synapse transmission (Feller et al., 1996) and then by glutamate (Maccione et al., 2014) propagate from the RGCs to the SC, dLGN, and V1 (Ackman et al., 2012) and help to refine topographic maps. Any interference with this spontaneous signaling pattern results in a disrupted RF refinement (Huberman et al., 2003; McLaughlin et al., 2003; Pfeiffenberger et al., 2006; Xu et al., 2011; Burbridge et al., 2014).

The topographic maps in V1 arise from the dLGN and SC axonal projections and are guided by chemotropic factors similar to those mapping the retinogeniculate and retinocollicular projections (Ackman et al., 2012; Zhao et al., 2013b). Reciprocally projecting corticothalamic neurons may also contribute to the targeting/mapping of dLGN projections to V1 (Molnár and Blakemore, 1995). The topographic organization of extrastriate visual areas is presumably mapped by projections from V1 and (Marshel et al., 2011; Garrett et al., 2014), however little work has been done in this area of research.

1.1.3 Receptive fields, what are they and why do they matter?

Visual receptive fields (RFs) are the currency that sensory neurons in the brain use to represent our world. Each neuron in the brain that receives visual input is responding to a small, restricted part of the visual field and the visual regions of the brain knit each of these individual

parts into the coherent image of our visual world. This coherent image is informed by a number of the aspects of the visual system that have already been discussed including retinotopic mapping, binocularity, and parallel processing of the various features of visual stimuli. RFs encode/represent each of these properties and are as crucial to our visual display of the world around us as are pixels displaying an image on a digital screen.

Neurons throughout the visual pathway have RFs that differ in size, structure, and complexity. The structure of RFs in the retina and thalamus can be described as two concentric circles with two alternating forms of a center-surround functional organization. On-center/off-surround RFs detect spots of light surrounded by a darkened background such as the fireflies in a dark field, and off-center/on-surround RFs detect dark spots surrounded by bright backgrounds such as a distant bird in the daytime sky (Kuffler, 1953). This organization allows them to detect discontinuities in the dispersion of light detected across the retina and is primarily useful for identifying the edges of objects (Deaglan, 2015). RFs with a center-surround organization are commonly detected in neurons in LGN and SC, but rarely detected in V1.

In V1, RFs are more complicated and have greater diversity than in the retina or thalamus. Rather than being concentric and circular, RFs in V1 are elongated and parallel, and can be classified as belonging to either simple or complex cells (Hubel and Wiesel, 1959, 1962) (see (Martinez and Alonso, 2003) for review). The RFs of neurons in V1 selectively detect many characteristics of visual stimuli, including; luminance contrast, stimulus velocity, stimulus size, color, direction of movement, line orientation, retinal disparity, and spatial frequency (frequency of dark and light contrasting stripes in a degree of visual space). V1 neurons can have RFs that are either sharply tuned (fail to detect selective stimuli if they are slightly off from the preferred detection criteria) or broadly tuned (respond to a wide range of detection criteria). The

development of these RF tuning properties is essential for normal visual function, and is an area of extensive study for the visual neuroscience community.

1.1.4 Distinct functional circuitries and processing streams

Beginning in the retina, unique features of visual scenery are processed in parallel by independently activating any one of the 30+ subtypes of RGCs (Baden et al., 2016). As previously described, these RGCs optimally respond to the presence of certain visual features and can then project to several different subcortical areas (Huberman et al., 2008b; Dhande et al., 2015). After innervating those distant targets, RGCs are further sorted (by cell type) into the distinctive layers of LGN or SC. This ordering, in conjunction with the laminar specific organization of target neuron dendrites, cell bodies, or both, in SC and dLGN, results in a robust parallel processing system for different visual features across all locations within the retinotopic map.

1.1.4.1 Retinal ganglion cell classes and subtypes

RGCs are classified by their morphology and function, and the nomenclature is often found to be species specific, perhaps due to species differences in eye architecture. For example, in cats the three main classes of RGC in the retina are called W, X, or Y cells defined by the differences in their response properties (Enroth-Cugell and Robson, 1966). Descriptions of RGC morphology resulted in 3 categories called α , β and γ cells (Boycott and Wässle, 1974). In primates three functional classes of RGCs were described and referred to as P, M, and bistratified cells (De Monasterio and Gouras, 1975).

X|P| β : 55% of total | medium sized cells (10-15 μm) | small dendritic fields | transmits color, detailed form information

Y|M| α : 5% of total | largest type (>35 μm) | broad dendritic fields | responds to rapid changes in spatial information

W|K| γ : 40% of total | smallest type (<10 μm) | broadest dendritic field | responds to directional movement

1.1.4.2 Parallel processing in the visual pathways

In most mammals, RFs of RGCs and LGN neurons exhibit a center-surround organization (on-center off-surround/off-center on-surround) (Hubel and Wiesel, 1959; Briggman et al., 2011). These simple On/Off discrimination parameters are carried through the visual pathway where additional features of the detected object, such as orientation and direction of movement are coded. Although stimulus direction and orientation are encoded later on (V1 and higher extrastriate areas) in primates (Scholl et al., 2013), recent evidence suggests that some RGCs in mice may also be orientation selective (Nath and Schwartz, 2016), suggesting that some neurons in dLGN may receive that property directly from the retina, rather than or in addition to feedback or post processing from V1.

Surprisingly, orientation tuning maps that do not derive from V1 have also been recently discovered in SC in mice. Indeed, large patches of retinotopic columns are tuned to specific orientations (Feinberg and Meister, 2014), though the maps do not appear to represent all orientations evenly. The purpose of these orientation columns has yet to be discerned, though logic would suggest that they might enable orientation hotspots (areas responsive to certain stimulus orientations in the visual field) that direct eye or head movement.

1.1.4.3 Two-streams model

Higher (extrastriate) cortical processing of visual information has been described by the two-stream theory in non-human primates (Livingstone and Hubel, 1988; Goodale and Milner, 1992). This model argues for two distinct visual systems functioning as parallel pathways; the ventral “what” pathway for visual object identification and recognition, and the dorsal “where” pathway for processing spatial location and motion. Some interaction does occur in order to provide an integration between the two disparate systems (Milner and Goodale, 2006), and the tuning of individual neurons is not as strictly dichotomous as initially proposed (Malpeli et al., 1981; for review see Schiller, 1996).

The ventral stream receives its primary input from the P cell layer of the LGN and projects to layers 4, 3, and 2 in V1 (Lamme et al., 1998). From there the ventral stream projects to extrastriate areas V2 and V4 of the inferior temporal cortex, with each visual area containing a full representation of the visual field, and with each step of processing conferring more detail to the perceived visual image. Ventral stream processing is significant for providing an overall description of the visual world, but it is perhaps most important for processing the significance of the individual elements comprising it. Damage to the ventral stream signaling pathway can result in the impaired identification of faces, or facial expressions (Tsao and Livingstone, 2008; Kravitz et al., 2013). Surprisingly, individual neurons in the inferior temporal cortex can respond selectively to stimulus identity, for example to a familiar face, or even to the written name of the identified stimulus (Quiroga et al., 2005).

The dorsal stream connects retina/LGN/V1 to the parietal cortex and is primarily important for spatial awareness and the guidance of physical actions (such as reaching) within

visual space. Spatial attention is another critical function of the parietal cortex; lesions to the parietal cortex result in contralateral neglect of visual, auditory, and tactile stimuli (Mishkin et al., 1983). Like the ventral stream, the dorsal stream can aid in object recognition, but only for objects that are novel, unconventional, or challenging in some way (Chao and Martin, 2000; Konen and Kastner, 2008; Almeida et al., 2010). Shape recognition and stimuli/purpose association are at the core of this recognition process, although the ventral stream also seems to have a role in mediating shape recognition and may influence this processing in the dorsal stream (Serenio and Maunsell, 1998).

Interestingly, it appears that some forms of visual perception can bypass V1 and the dorsal/ventral stream signaling pathways altogether. Postrhinal cortex (POR) is a part of the visual cortex responsible for discriminating moving stimuli (Glickfeld and Olsen, 2017), and receives input from V1. Surprisingly, inactivating V1 via optogenetic light pulses in mice does not impair visual responses in POR, suggesting that input directly from the SC, rather than V1 through the traditional visual circuit, drives activity in POR (Beltramo and Scanziani, 2019). These findings could have implications for understanding the phenomenon “blindsight” in which people become perceptually blind because of damage to V1 but are still able to interpret the position of objects and navigate obstacles even though they cannot consciously perceive them (Leopold, 2012).

1.1.5 Activity independent and dependent development in the visual system

An important question in developmental biology concerns the relative contributions of intrinsic factors and the external environment to individual traits. Studies of the mammalian visual system have provided several examples of activity-dependent and -independent events

during development. For the visual system, activity can come from spontaneous firings of neurons or from visual stimuli. Experience-independent and -dependent developmental processes largely correspond to two different stages of development: the inceptive patterning of circuits prior to eye opening, and their subsequent maturation and refinement, respectively.

1.1.5.1 Defining the roles of activity

The roles played by activity in shaping the visual system are varied. **Instructive activity:** can be either spontaneous or stimulus driven, is necessary to either establish or alter a neuronal structure or function, and is influenced by activity levels (more activity drives more change). For example, kittens reared in a single orientation environment develop with a higher percentage of cortical area representing the experienced orientation compared to other orientations (Blakemore and Cooper, 1970; Sengpiel et al., 1999), suggesting that visual experience instructs orientation selectivity in V1. **Permissive activity:** can affect structural or functional development only if a specific threshold of activity is reached, but further increases in activity beyond that threshold do little to influence or instruct development. Direction selectivity is not present at birth in ferret V1, but cells are biased to weakly respond to certain directions of stimulus movement (Li et al., 2008). Raising ferrets so that they only experience a single motion of direction enables cells biased to the experienced direction of motion to increase their direction selectivity (Van Hooser et al., 2012). Indeed, brief unpatterned optogenetic activity in ferret V1 is sufficient to elicit the rapid emergence of direction selectivity (Roy et al., 2016), suggesting that direction preference is already present in cells and activity is permissive for its development,

1.1.5.2 Intrinsic (experience independent) development

The timeline for visual system development is useful for understanding experience-independent, spontaneous activity dependant, and experience dependent development. Logically this timeline should have roughly the same sequence as the signaling pathway for translating visual sensory information into a perceived image. The anatomical and physiological maturation of the retina (Firth et al., 2005) precede the architectural formation of the LGN (Weliky and Katz, 1999), which precedes the structural and functional development of V1 (Wong, 1999; Katz and Crowley, 2002). This timeline leads to the possibility that the LGN requires some form of input from the retina and correspondingly, V1 organization is directed by signals from LGN, otherwise they could form simultaneously.

During the early stages of visual development, RGCs and other retinal cells are born, differentiate, and project – both within the retina and toward the brain – without any experience driven activity (Young, 1985; Wetts and Fraser, 1988; Turner et al., 1990). RGC axons migrate away from the eyes and are held together in a close bundle by inhibitory guidance cues Sema5A and Slit2 secreted from intrafascicular glial cells of the optic nerve (Silver, 1984; Plump et al., 2002; Oster et al., 2003). The optic nerve is guided by chemo-attractive signaling at the optic chiasm (Plump et al., 2002; Plachez et al., 2008) where the majority of RGCs cross the midline to the contralateral side (Kennedy et al., 1994; Erskine et al., 2011). From there the RGCs are guided along the optic tract towards their major targets – the SC and LGN – by a number of chemoaffinity molecules (Ringstedt et al., 2000; Ichijo and Kawabata, 2001; Becker et al., 2003; Gordon et al., 2010). After reaching their targets the innervating RGCs topographically map themselves via the ephrin system as has previously been discussed, and further segment themselves into the layers of the LGN. Thalamocortical connections are made in layer 4 of V1,

forming the ocular dominance bands. Although these examples of visual development all happen in an experience-independent manner (before the onset of visually evoked activity), they also require intrinsic, spontaneously generated activity (Goodman and Shatz, 1993).

1.1.5.3 Spontaneous activity in development

Spontaneous activity in the visual system begins early in postnatal life. In mammals, a wave of spontaneous activity propagates across the retina of each eye approximately every minute (Wong et al., 1993; Wong, 1999). There are 3 types of these “retinal waves”, the first of which to appear are Stage I waves, which are propagated through gap junctions and occur before birth (Firth et al., 2005). Stage II waves are dependent on nicotinic cholinergic receptors, initially propagate over large areas, then become smaller and more dense as inhibitory signaling begins to mature around P7 (Feller et al., 1996; Maccione et al., 2014; Arroyo and Feller, 2016). At Stage III (after P10), glutamatergic synapses are responsible for retinal waves that persist until a few days after eye opening. Spontaneous activity continues throughout life in the visual system, but the activity is no longer structured in propagating waves.

Retinal waves are important for many aspects of normal development of the visual system. Retinal waves appear to instruct the lamination of the LGN (Stellwagen and Shatz, 2002), and are necessary for them to form correctly in the first place. Blocking all spontaneous and visually-evoked activity in the retina using localized tetrodotoxin (TTX) injections results in disrupted (but not absent) topographic map formation (Thompson and Holt, 1989) and RGC layer segregation in LGN (Shatz and Stryker, 1988). Genetically deleting the β 2-subunit of the nicotinic acetylcholine receptor (nAChR) disrupts the Stage II waves without affecting Stage I or III, and yet results in targeting errors and expanded terminal branches in SC (McLaughlin et al.,

2003), LGN (Grubb et al., 2003), and V1 (Cang et al., 2005b), leading to enlarged RFs. Stage III waves result from the sequential recruitment of adjacent RGCs with opposing light responses (On vs Off) (Kerschensteiner and Wong, 2008), a process that suggests an overall role for Stage III waves in forming on-off RF sub-regions in the retina. Although a causal relationship has yet to be established, orientation selectivity in V1 (which is thought to depend on separate on-off RF sub-regions) matures rapidly around the time of eye opening and is independent of vision in rodents (Sarnaik et al., 2014; Hoy and Niell, 2015), suggesting a role for Stage III retinal waves in their development.

1.1.5.4 Experience-dependent development

Stimulus-evoked activity is limited early in visual development. Very little light penetrates the mammalian uterus (Rao et al., 2013), and many animals are born with their eyes closed. Although some stimulus-evoked activity can occur through the eyelids (Krug et al., 2001; Colonnese and Khazipov, 2010), significant visual experience does not occur until eye opening (P10-14 in mice and many other rodents, approximately P30 in ferrets), after most of the early retinofugal connections are made in SC and LGN, and geniculocortical connections are made to V1. This timeline of development suggests that stimulus-evoked activity may play a more significant role in shaping the visual pathway at levels higher than SC and LGN.

Once the initial patterning of the visual system has been established by intrinsic spontaneously generated activity, the fine tuning of the topographic maps and pruning of RF response properties are guided by visual stimuli present in the environment. For example, in V1, orientation selective maps (columns of cells that respond to particular stimuli orientation) can form without any vision (Crair et al., 1998; White et al., 2001), although the final level of

maturation can vary between species, especially in the absence of vision (Buisseret and Imbert, 1976; Chapman and Stryker, 1993; White et al., 2001). Similarly, orientation selective cells in rodent V1 (which lacks a distinct columnar organization) also develop without vision (Rocheport et al., 2011; Ko et al., 2013; Sarnaik et al., 2014), but substantially mature in the weeks immediately following eye-opening (Rocheport et al., 2011; Hoy and Niell, 2015). In all studied species orientation selectivity requires experience for proper maintenance (Fagiolini et al., 1994; Crair et al., 1998; Kang et al., 2013a), is plastic to changes induced by both artificial visual stimulation (Weliky and Katz, 1997; Kreile et al., 2011), and environments expressing only a single orientation (Sengpiel et al., 1999). Further evidence supporting experience-driven fine-tuning is that vision is required during the formation of ocular dominance columns in V1 to enhance and maintain the corresponding orientation preference from each eye that is already present at eye opening (Wang et al., 2010; Wang et al., 2013; Sarnaik et al., 2014), and the development of visual acuity in binocular V1 is delayed by dark rearing (Kang et al., 2013a). These results suggest that experience can play an instructive role in modifying the orientation preference of RFs in V1, and is essential for fine tuning the previously established circuits.

Although visual experience is important for development, the quality of that experience can have a substantial effect on how neural circuits are shaped. Studies that prevented visual experience using binocular eyelid suture in place of dark rearing quickly found that, rather than blocking all light, the procedure merely blocks only patterned visual stimulation (no visual edges are experienced) (Mower et al., 1981a). This kind of visual experience resulted in enlarged (unrefined) RFs, reduced visual responsiveness, (Mower et al., 1981a), a misalignment of the eyes (Sherman, 1972), and disrupted orientation tuning (Crair et al., 1998). Dark rearing results in a less profound retardation of visual development, and can often lead to some recovery of

function later in development, whereas binocular eyelid suture results in permanent detrimental changes that cannot be overcome (Mower et al., 1981a). These results suggest that diffuse visual activity is not sufficient for mediating experience-dependent development of the visual system, but rather that patterned visual activity is required (Ruthazer and Aizenman, 2010).

1.1.6 Critical vs. sensitive periods

A key issue in studying the effects of environmental experience on development is to understand how and when exposure is the most influential. This concept is generally referred to as a critical or sensitive period. Although “critical periods” and “sensitive periods” are often used interchangeably, they differ in fundamental ways. For example, the sensitive period is a broad term that is often used to describe the effects that experience has on the brain during limited periods in development (Knudsen, 2004). Notably, if a key experience is absent during a sensitive period, it may be difficult, without extraordinary effort, to redirect development along a normal course; even then, function in the affected modality may not fully recover. In contrast, if a key experience fails to occur during a critical period, development and function can be permanently affected, whereas some functional recovery is possible with sensitive period-dependent development.

Although the term “critical period” has persisted throughout the popular science lexicon, it’s important to note that the majority of phenomena it is used to describe throughout the entirety of cognitive/behavioral development are likely reflective of sensitive periods. In contrast, the development of the visual system has several examples of true critical periods that have been extensively studied. Monocular deprivation during early development results in a major shift (98%) in V1 neuron responses from the deprived eye to the non-deprived eye (Wiesel

and Hubel, 1963b), suggesting a competitive process of ocular dominance column formation in V1. Importantly, follow up studies identified that these effects were restricted to the first 3 weeks of development, the “critical period” for ocular dominance plasticity. Even a short period (3-4 days) of monocular deprivation during this critical period leads to a lasting and largely irreversible decline in the responses to the deprived eye, whereas far longer periods of monocular deprivation in an adult cat have little to no physiological impact (Hubel and Wiesel, 1970). Although it is important to distinguish between sensitive and critical periods, the mechanisms differentiating them are not well understood and require further examination.

It is important to note that critical periods occur in a parallel (between modalities) and sequential (within modalities) manner during development; thus, there will be multiple, cascading critical periods for different neural circuits that may overlap. Sequential critical periods occur in cases that “lower” brain areas (those proximal to stimulus detection) mature before “higher” areas (those upstream involved with higher order processing). For example, in the mouse visual system, retinocollicular connections stabilize their orientation tuning before V1 neurons do (Seabrook et al., 2017). In auditory development, development of tonotopy (the topographical mapping of sound frequencies in auditory cortex) precedes language acquisition in humans, because the maturation of upstream areas involved with basic sound perception are required before those sounds can be comprehended as words (Werker and Hensch, 2015). Interestingly, some modes of higher order processing do not seem to be dependent on experience during early critical periods. For example, congenitally blind children who are surgically given sight do not have innate face schemas, but are able to learn to differentiate faces with a high degree of proficiency through natural visual experience (Gandhi et al., 2017).

It is well accepted that critical periods function as windows in time in which synaptic connections are fine-tuned. After critical periods close, synaptic connections are resistant to change, even with significant changes to the environment (Hensch, 2004). Although critical periods can be a time of progress, they are also a time of vulnerability. For example, failure to correct congenital cataracts or a “lazy eye” in early life can lead to amblyopia (permanent cortical blindness of retinal input from the affected eye) even though the eye itself is healthy. Similarly, loss of auditory input from chronic ear infections during an early critical period can detrimentally affect language acquisition in children (Werker and Hensch, 2015). These consequences highlight the terminal nature of critical periods, along with the importance of quality sensory experiences during early windows in neural development. However, the mechanisms controlling the onset and closure of critical periods are not yet understood. Identifying these mechanisms will illuminate our understanding of the negative outcomes associated with failures in these processes, and generate insights into how these outcomes can be treated.

1.1.7 Role of activity in receptive field refinement

RFs are a critical feature for visual stimulus detection, perception, and higher order processing. RFs of neurons are organized topographically throughout the visual pathway and organize neuronal response properties that allow selective detection of certain aspects of visual stimuli. These response properties can be inherent to the neuron - forming independent of activity, or they can be influenced by its inputs. Either way, classic studies have demonstrated that molecular cues and spontaneous activity are both essential in the early formation of RF properties, but the refinement and maturation of RFs is guided by visual experience. However,

much work remains to be done in order to elucidate the mechanisms underlying the processes stabilizing RFs in adulthood.

Many RF properties have already been discussed throughout this chapter, including orientation and direction selectivity; however the overall discrimination of these (and other) visual features is ultimately limited by visual acuity. Acuity is an important limiting factor for processing binocular disparity and identifying high frequency contrast stimuli, especially in V1 (Sceniak et al., 1999; Nienborg et al., 2004). Visual acuity is poor in mammals at eye opening; rats, for example, double their overall cortex-dependent visual acuity between eye opening and adulthood (Fagiolini et al., 1994), a sequence that coincides with the refinement of RF size.

The progressive refinement of RF size is an activity dependent process (Thompson and Holt, 1989; Huang and Pallas, 2001a; Chandrasekaran et al., 2005), and several early reports suggested that RFs in SC and V1 fail to refine in dark reared (DR) rodents (Fagiolini et al., 1994; Gianfranceschi et al., 2003). Behavioral measures in DR adults also show reductions in visual acuity (Timney et al., 1978). In contrast, previous work by my research group determined that these early findings were misinterpreted due to a failure to examine earlier ages.

In contrast to the critical role of visual experience for several features of RF development, vision is not necessary for RFs to refine in size in hamster SC (Carrasco et al., 2005) or V1 (Balmer and Pallas, 2015a). In hamsters that have been DR from birth, RFs refine normally by P60, but refinement is not maintained and they re-enlarge by P90. Providing brief (35 hours) visual experience during an early critical period (P33-P40) is sufficient to maintain RFs of DR hamsters in their refined state beyond P90, but experience outside of the critical period cannot rescue RFs that have already re-enlarged as a result of dark rearing (Carrasco and Pallas, 2006; Balmer and Pallas, 2015a).

Loss of RF refinement in DR hamsters was accompanied by a loss of inhibition in SC and V1 (Carrasco et al., 2011). In the adult brain, inhibitory signaling is caused by the neurotransmitter gamma-Aminobutyric acid (GABA), and its two high affinity receptors; the ligand-gated ion channel GABA_A and the metabotropic GABA_B receptor. Chronic dark rearing results in reduced GABA expression and decreased GABA_A receptor mediated inhibitory signaling in adult SC (Carrasco et al., 2011). Further work also revealed a dysregulation in GABA_B receptor-dependent short-term depression in the SC of DR adults (Balmer and Pallas, 2015b).

These results provided us with a compelling reason to examine the mechanisms underlying the initial effect of visual-evoked activity during the critical period (Chapter 2) and [missing verb] how visual experience could be mediating the maintenance of refined RFs in adulthood (Chapter 3).

1.2 Proposed role of neurotrophins in RF development

Sensory activity could influence development via the activity-dependent expression of neurotrophic factors. Neurotrophic factors (*aka* neurotrophins) are a family of proteins that promote the survival, development, and function of neurons throughout the central nervous system (CNS) (Barbara, 2006; Reichardt, 2006; Park and Poo, 2013a). In the mammalian CNS, neurotrophins include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4) (Huang and Reichardt, 2001). These growth factors are secreted by target tissues and typically function by activating tropomyosin-related kinase (Trk) receptors;- NGF:TrkA, BDNF:TrkB, NT-3/NT-4:TrkC- that prevent the associated neuron from initiating programmed cell death – allowing neuronal survival (Bothwell, 1995;

Arevalo and Wu, 2006). In addition, BDNF is well known to be a regulator for the maturation of inhibitory synapses (Rutherford et al., 1997; Hanover et al., 1999; Gao et al., 2014).

Environmental enrichment (a means of increasing sensory-motor activity, social interactions, and general cognitive activity) promotes the expression of BDNF throughout the brain (Bartoletti et al., 2004; Sale et al., 2007), which is advantageous for learning and recovery of lost function (Tognini et al., 2012; Peruzzaro et al., 2013). BDNF is essential in regulating neuronal plasticity (Allen et al., 2013) and is a major focus of research in treating ailments of the brain such as Alzheimer's disease (Nagahara et al., 2009), stroke (Schäbitz et al., 1997), and traumatic brain injury (Blaha et al., 2000). Experience-driven activity could be selective or permissive for RF maintenance via the activity-dependent expression of BDNF.

The overexpression of BDNF in young mice rescues adult V1 from the detrimental effects of chronic dark rearing (including RF refinement) (Gianfranceschi et al., 2003), and can promote the recovery of visual acuity in adult rats that were monocularly deprived in development (Tognini et al., 2012). These experiments suggest that activity-driven BDNF synthesis is an important modulator of development in V1; however, its regulatory effects in different parts of the visual pathway have yet to be examined. In Chapter 2 I address this issue by studying how increased BDNF/TrkB activity during the critical period for RF size maintenance affects RFs in adult SC. I also examine several visually dependent behaviors that could be affected by the loss of RF refinement, and differentiate between the necessity of RF refinement and visual experience in mediating those differences.

1.3 Proposed mechanisms of receptive field size maintenance

The question of how visual experience during an early critical period can contribute to the stability of RFs several weeks later in development relates to how plasticity is restricted in adulthood. Once visual circuits are established and fine-tuned, plasticity could be detrimental to normal function. Reduced plasticity is useful in preventing sensory circuits from regressing, but also places limits on the potential recovery from injury and neurodegenerative disease. Studying how visual experience establishes and maintains refined RF circuits in SC in adulthood will inform novel theories about critical period regulation, how it can be reopened, and how maladaptive plasticity can be prevented.

1.3.1 The maintenance of inhibition could maintain RFs

Inhibition has an essential role in the developmental plasticity of V1. The role of inhibition in ocular dominance plasticity in particular has been extensively studied (Fagiolini and Hensch, 2000; Hensch, 2005b; Kuhlman et al., 2013) and changes in inhibition have been shown to affect both the opening and closing of its critical period (Fagiolini and Hensch, 2000). Dark rearing reduces inhibition in V1 (Benevento et al., 1992; Benevento et al., 1995; Morales et al., 2002), and extends the critical period into adulthood so that monocular deprivation can lead to changes in ocular dominance plasticity well beyond the normal juvenile critical period (He et al., 2006). This critical period prolongation can be halted by the artificial augmentation of GABA (Iwai et al., 2003) (Huang et al., 2010), which results in normal levels of inhibition, or accelerated by artificially inducing the decay of GABA signaling (Fagiolini et al., 2004). The critical period can also be extended indefinitely by delaying the maturation of GABA (Hensch et al., 1998), or reopened in adulthood by reducing GABAergic inhibition pharmacologically

(Harauzov et al., 2010). Together these results suggest that inhibition can play a large role in the maintenance of RFs during and after normal development. Identifying the mechanism(s) responsible for the loss of inhibition in DR adult SC is essential for understanding how to prevent maladaptive plasticity in adulthood.

Long-term synaptic plasticity is a phenomenon that occurs routinely throughout the brain (Malenka and Bear, 2004) where synaptic strength is altered and remains that way for at least 30 minutes and up to several hours. Long term plasticity involves two types of change in synaptic strength: long term potentiation (LTP) - an increase in synaptic strength, and long term depression (LTD) - a decrease in synaptic strength. Typically LTP and LTD occur via coincidence detection of activity between a pre and postsynaptic neuron mediated by *N*-methyl-d-aspartate (NMDA)-type glutamate receptors (Malenka, 1994). LTP occurs when a presynaptic cell “repeatedly and persistently” excites a postsynaptic cell (Hebb, 1949; Hebb, 2005), and LTD logically appears in the opposite manner, where a “reduction in frequency in the use of one set of synapses permits the other to take complete charge” (Stent, 1973). For example, in monocular deprivation studies, LTD has been observed occurring in V1 when deprived eye responsiveness is lost (Kirkwood et al., 1996; Frenkel and Bear, 2004; Crozier et al., 2007), and LTP occurs during the strengthening of the non-deprived eye responses (Kirkwood and Bear, 1994; Heynen and Bear, 2001), with interference in the molecular mechanisms underlying LTP disrupting this process (Hensch, 2005a). Although reliant on Hebbian signaling (LTP/LTD), a fair amount of synaptic scaling and homeostatic regulation is also necessary for changes in ocular dominance to occur (Espinosa and Stryker, 2012).

LTP is essential for the initial refinement of RFs in V1 early on in development, (Kirkwood et al., 1995; Maffei and Turrigiano, 2008), and appears to follow the overall pattern

of RF plasticity. For example, it is can be restricted in adult V1 by early visual experience (Kirkwood et al., 1996), main its ability to be expressed in adulthood by dark rearing (Kirkwood et al., 1995; Kirkwood et al., 1996), and is modulated by the strength of inhibitory signaling (Artola and Singer, 1990). Although one would assume LTP and LTD to be likely mechanisms underlying plasticity in SC, we previously found that dark rearing through the critical period reintroduced plasticity but did not generate any additional LTP or LTD (Balmer and Pallas, 2015b). Instead it reduced short-term (but not long-term) depression of excitatory synapses, suggesting a decrease in the availability of neurotransmitters for release. Recent work may provide an alternative explanation for our inability to detect LTP in DR adults. Brief visual exposure following sensory deprivation promotes the emergence of a NMDAR-independent form of LTP governed by mGluR5 signaling (Li et al., 2017a). This NMDAR-independent LTP is suggested to play a role in the establishment of normal RF properties, but it is transient and disappears shortly after novel visual experience, making it unclear at what age it is most relevant and how it may affect the long term stability of V1. Although these reports could potentially explain how RF plasticity returns in adulthood, they do not explain the decreased responses to inhibitory neurotransmitter previously observed in DR adult SC (Carrasco et al., 2011). Many possible explanations for the reduced inhibitory responses in DR adults are studied in Chapter 3 of this dissertation.

1.3.1.1 GABA_A receptor subunit composition

GABA_ARs belong to the superfamily of Cys-loop ligand-gated ion channels that comprises nicotinic acetylcholine (nACh) receptors, strychnine-sensitive glycine receptors and 5-hydroxytryptamine type-3 (5-HT₃) receptors. Receptors belonging to this family are

heteropentameric glycoproteins comprised of corresponding subunits that specifically recognize each other and conform around an intrinsic ion channel, which for GABA_ARs are permeable to Cl⁻ and to a limited extent, bicarbonate anions (Unwin, 1993). The composition/configurations of the individual subunits making up GABA_ARs can affect how well they function and is an avid area of research.

GABA_A receptors cause fast acting inhibition in neurons by acting as a ligand-gated channel for Cl⁻ into the cell. Our previous work indicates that these fast responses to a GABA receptor agonist were severely diminished in adult SC after dark rearing from birth (Carrasco et al., 2011). This loss of function could result from several changes in the development of the subunits comprising the pentameric structure of the GABA_A receptors. Five subunits (out of six- alpha, three-beta, three-gamma, one-delta, one-epsilon, and one-pi discovered so far) are arranged around a central pore with the primary configurations including 2 alpha, 2 beta, and a gamma subunit (Farrant and Nusser, 2005). During early development (dependent on species but in general – P20-30), a switch from the dominant alpha two to alpha one subunit reduces the delay in receptor activation and recovery time, significantly increasing inhibitory signaling strength (Okada et al., 2000). This development may provide a means of stabilizing inhibitory circuits in SC, and if this process were disrupted by early sensory deprivation it could potentially lead to maladaptive adult plasticity in adulthood.

Alternatively, subunit composition can affect receptor accumulation and membrane trafficking at inhibitory synapses (Jacob et al., 2008), potentially shifting phasic (synapse localized) receptors towards a more tonic (extrasynaptically localized) role. This would result in reduced total fast acting inhibition. Alpha1,2,3, beta2/3 and gamma2 incorporating GABA_ARs are predominantly mediating phasic inhibition, and are thus synaptically localized. It is

important to note however, that these receptors have dynamic mobility and go through a rapid exchange between extrasynaptic and synaptic receptor clusters (Jacob et al., 2005; Thomas et al., 2005). The alpha5 subunit is unique because it is localized and enriched extrasynaptically (Brünig et al., 2002) and is thus a conductor of tonic inhibition. Indeed, the deletion of alpha5 subunit will eliminate tonic conductance entirely in cultured hippocampal neurons (Caraiscos et al., 2004). Changes in alpha5 subunit expression and tonic inhibition in adulthood could account for the losses in GABA_AR function observed in SC and V1 after early dark rearing (Carrasco et al., 2011; Balmer and Pallas, 2015a).

1.3.1.2 Intracellular trafficking of GABA_A receptors

GABA_A receptor trafficking is partially regulated by endocytosis: the controlled removal of receptors in the membrane. They are subsequently reinserted into the membrane or undergo lysosomal degradation after longer periods (Kittler et al., 2004). Interactions between GABA_AR β 1–3 subunits and huntingtin associated protein 1 (HAP1) determine whether endocytosed GABA_ARs are recycled or reinserted (Kittler et al., 2004). This process of endocytosis can have a great deal of influence on inhibitory and excitatory signaling in neuronal networks (Kanematsu et al., 2007; Leidenheimer, 2008). It is unknown whether dysregulation of GABA_A receptor endocytosis and reinsertion is present during experience-driven maturation of sensory circuits; however it is linked with several degenerative diseases that involve failings in GABAergic inhibition, much like the loss of RF maintenance in DR adults. For example, in a mouse model of Parkinson's disease, the reduction of the trafficking protein kinesin binding 1 (Trak1) (a homolog of HAP1) (Li et al., 1995), results in marked reductions in the expression of GABA_ARs in the CNS (Gilbert et al., 2006). In studies of Alzheimer's disease, GABA_ARs are less sensitive

to GABA (Limon et al., 2012), and amyloid- β (a hallmark pathology in Alzheimer's disease) weakens synaptic inhibition by down-regulating GABA_ARs through endocytosis (Ulrich, 2015). An increase in the rate of GABA_A receptor endocytosis in primary neurons in SC could also underlie the loss of inhibition observed in dark reared adult hamsters.

The equilibrium between the lateral diffusion, insertion, internalization and recycling of GABA_AR in the plasma membrane governs the strength of GABAergic synapses. Flaws in GABA_AR trafficking have been indicated as triggers of GABAergic dysfunction in several neuronal pathological conditions (for review see Hines et al., 2012). Studying the mechanisms that lead to stabilizing GABA_A receptor trafficking in development could be instrumental in designing treatments for psychiatric and neurodegenerative diseases.

1.3.2 Membrane scaffolding proteins

One mechanism influencing the accumulation and confinement of GABA_A receptors at postsynaptic sites is the membrane scaffolding protein gephyrin (Kneussel et al., 1999; Sun et al., 2004; Jacob et al., 2005; Tretter et al., 2008). Decreased expression of gephyrin results in less clustering of GABA_A receptors (Essrich et al., 1998) and more overall mobility at the synapse (Jacob et al., 2005). Increasing gephyrin expression chemically *in vitro* and by an experience-dependent plasticity protocol *in vivo* in developing V1 neurons results in greater GABA_A receptor accumulation at synapses and increases inhibitory LTP (Petrini et al., 2014). There is also evidence of gephyrin-independent clustering, as gephyrin KO mice still possess clustered GABA_A receptors along with miniature IPSCs (postsynaptic responses to passive (non-action potential) neurotransmitter release) (mIPSCs) (Kneussel et al., 2001; Levi et al., 2004; Zita et al., 2007). Nevertheless, if gephyrin expression was decreasing in SC following sensory

deprivation, it could be responsible for reduced clustering of GABA_A receptors and lower levels of GABAergic inhibition.

PSD-95 is the primary excitatory (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)) receptor scaffolding protein in neurons, and functions largely in the same way as gephyrin does for GABA receptors. Although it does not have a direct impact on GABA_A receptor function, PSD-95 has been shown to have an influence on visual plasticity. For example, PSD-95 expression in SC increases rapidly at eye opening and is crucial for the emergence of *N*-methyl-D-aspartate receptors (NMDAR)-dependent LTP (Zhao et al., 2013a), a feature that requires the unsilencing (insertion of AMPA receptors) of silent synapses (synapses that only have NMDA receptors along the postsynaptic membrane). In addition, mice lacking PSD-95 have lifelong ocular dominance plasticity in V1 that results from an increase in the overall expression of silent (AMPA-free) synapses, but completely normal inhibitory tone (Huang et al., 2015b). Considering the role PSD-95 plays in silent synapse maturation and critical period gating it deserves recognition as a possible mechanism underlying maladaptive RF plasticity in the adult visual system.

1.3.3 NMDA receptor subunit composition

Excitatory plasticity may also contribute to enlargement of RFs during DR (Huang and Pallas, 2001b). LTP and LTD are two of the most extensively studied models of synaptic regulation underlying experience-dependent cortical plasticity (Tsumoto, 1992; Bliss et al., 2003). In V1, LTP and LTD have been studied within all cortical layers, though their mechanisms, consequences, and rules of induction have been mainly studied in layer 2/3 pyramidal cells (Artola and Singer, 1987; Taniguchi et al., 1989; Kirkwood and Bear, 1994;

Heynen and Bear, 2001; Wang and Daw, 2003; Cooke and Bear, 2010). These studies established that LTP/LTD induction is Hebbian (cells that fire together wire together), depends on NMDAR activation (Bear et al., 1992; Kirkwood and Bear, 1994), and is guided by visual experience. Visual deprivation from birth enhances NMDAR-dependent LTP in layers 2/3 of V1 (Kirkwood and Bear, 1994; Kirkwood et al., 1995; Guo et al., 2012). A developmental switch from the NR2B to NR2A subunit of NMDARs occurs alongside the decline in visual plasticity in V1 (Gordon and Stryker, 1996; Erisir and Harris, 2003). Dark rearing also disrupts the substitution of the NR2A subunit for the NR2B subunit that normally occurs postnatally in V1, limiting NMDAR-dependent excitatory plasticity (due to the shorter open time of NR2A) (Carmignoto and Vicini, 1992b; Philpot et al., 2001). Thus, examining changes in the NR2A/NR2B subunit composition could provide an explanation for how early visual experience prevents adult plasticity in adulthood and maintains RF refinement. Reduced NR2A expression relative to NR2B could cause RFs to expand through potentiation of excitatory synapses.

1.3.4 Chloride pump ratio

Inhibitory GABAergic signaling in neurons is dependent upon the intracellular chloride (Cl^-) concentration. The $\text{K}^+ \text{Cl}^-$ co transporter (KCC2) is responsible for regulating intracellular Cl^- in mature adult neurons via an outward K^+ current (Rivera et al., 1999), and also regulates the formation, function, and plasticity of glutamatergic synapses (Li et al., 2007; Gauvain et al., 2011; Chevy et al., 2015). Early in development GABA_A receptors are excitatory because the $\text{Na}^+ \text{K}^+ 2\text{Cl}^-$ co transporter 1 (NKCC1) (which mediates Cl^- uptake) is dominant, and during the first several weeks after birth is replaced by KCC2 as the dominant Cl^- pump in the brain, causing GABA_A receptor activation to hyperpolarize neurons. Recent findings reveal that in V1,

the developmental switch from NKCC1 to KCC2 occurs at the same time as a period of BDNF/TrkB mediated synaptic imbalance – a crucial critical period for the transition of immature neurons to a more mature state of functionality (Zhang et al., 2018). There is also evidence linking alterations in chloride homeostasis to the impairment of GABAergic inhibition (Rivera et al., 2004). Down-regulation of KCC2 results in increased intracellular Cl^- and thus, generates a positive shift in the reversal potential for GABA_A receptors, a phenomenon linked to epilepsy in hippocampal slices. Indeed, in human studies, the presence of a rare variant of KCC2 increases the risk of developing epilepsy (Kahle et al., 2014; Puskarjov et al., 2014) and other degenerative diseases. If the ratio of KCC2:NKCC1 was decreasing in DR adult SC, then GABA_A receptors would have less driving force and provide reduced inhibition, perhaps resulting in a re-expansion in RFs in adulthood

1.4 Why investigate Syrian hamsters?

Syrian hamsters have been extensively studied in the field of developmental neurobiology for the last fifty years (Schneider, 1969; Chalupa and Rhoades, 1978; Rhoades and Chalupa, 1978; Mort et al., 1980), and especially so for studies of the SC and visual development (Mort et al., 1980; Udin and Schneider, 1981; Pallas and Finlay, 1989; Thompson and Holt, 1989; Choi et al., 2009). The original work examining the necessity for visual experience in maintaining, rather than facilitating RF refinement in SC (Carrasco et al., 2005) and V1 (Balmer and Pallas, 2015a) was accomplished in Syrian hamsters. Compared to other commonly studied lab mammals, Syrian hamsters have the shortest gestation period (15-18 days) (Bond, 1945) and are thus more immature in their development at birth. Syrian hamsters also have a large litter size and have little problem reproducing in a laboratory environment (Fritzsche et al., 2006).

These reproductive factors and the high visual acuity of hamsters compared to other rodent species (Langley, 1985) make Syrian hamsters a favorable species for studying visual development and the experience dependent maintenance of RF maturation.

1.5 Clinical importance

Much of our adult function and behavior reflects the neural circuits sculpted by experience in early development. At no other time in life does the surrounding environment so potently shape brain function including basic motor skills, sensation, and even higher cognitive processes like language or emotion. This ability to shape learning waxes and wanes with age and carries an impact far beyond neuroscience, including how we approach education, the treatment of developmental disorders, and strategies for recovery from traumatic brain injury.

**2 TRKB ACTIVATION DURING A CRITICAL PERIOD MIMICS THE
PROTECTIVE EFFECTS OF EARLY VISUAL EXPERIENCE ON PERCEPTION
AND THE STABILITY OF RECEPTIVE FIELDS IN ADULT SUPERIOR
COLLICULUS**

David B. Mudd, Timothy S. Balmer, So Yeon Kim, Noura Machour, and Sarah L. Pallas

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2.1 Abstract

During a critical period in development, spontaneous and evoked retinal activity shape visual pathways in an adaptive fashion. Interestingly, spontaneous activity is sufficient for spatial refinement of visual receptive fields in superior colliculus (SC) and visual cortex (V1), but early visual experience is necessary to maintain inhibitory synapses and stabilize RFs in adulthood (Carrasco et al. 2005, 2011; Carrasco & Pallas 2006; Balmer & Pallas 2015a). In visual cortex (V1), brain-derived neurotrophic factor (BDNF) and its high affinity receptor TrkB are important for development of visual acuity, inhibition, and regulation of the critical period for ocular dominance plasticity (Hanover et al., 1999; Huang et al., 1999; Gianfranceschi et al., 2003). To examine the generality of this signaling pathway for visual system plasticity, the present study examined the role of TrkB signaling during the critical period for RF refinement in SC. Activating TrkB receptors during the critical period (P33-40) in DR subjects produced normally refined RFs, and blocking TrkB receptors in light-exposed animals resulted in enlarged adult RFs like those in DR animals. We also report here that deprivation- or TrkB blockade-induced RF enlargement in adulthood impaired fear responses to looming overhead stimuli, and negatively impacted visual acuity. Thus, early TrkB activation is both necessary and sufficient to maintain visual RF refinement, robust looming responses, and visual acuity in adulthood. These findings suggest a common signaling pathway exists for the maturation of inhibition between V1 and SC.

2.2 Significance Statement

Receptive field refinement in superior colliculus (SC) differs from more commonly studied examples of critical period plasticity in visual pathways in that it does not require visual experience to occur; rather spontaneous activity is sufficient. Maintenance of refinement beyond

puberty requires a brief, early exposure to light in order to stabilize the lateral inhibition that shapes receptive fields. We find that TrkB activation during a critical period can substitute for visual experience in maintaining receptive field refinement into adulthood, and that this maintenance is beneficial to visual survival behaviors. Thus, as in some other types of plasticity, TrkB signaling plays a crucial role in RF refinement.

2.3 Introduction

As sensory pathways transition from a highly plastic state early in life to a stable state in adulthood, stimulus tuning properties are progressively sharpened through neural activity-dependent plasticity and are then maintained in that state. Much of the investigation into the regulation of critical periods has centered on the development of visual system connectivity, particularly on the developmental increase of GABAergic inhibition. Development of inhibition in primary visual cortex (V1) is controlled by experience driven BDNF signaling through its high affinity receptor TrkB (Huang et al., 1999; Huang and Reichardt, 2003; Jiang et al., 2005; Gao et al., 2014), and has been shown to substitute for experience in the context of ocular dominance tuning in transgenic mice (Gianfranceschi et al., 2003). Here we address the generalizability of TrkB signaling as a mechanism underlying critical period regulation across different tuning properties and visual regions.

Receptive field (RF) refinement is an essential step in visual system development. Visual experience is required for development of acuity in monkeys (Regal et al., 1976; Teller et al., 1978), cats (Timney et al., 1978; Derrington and Hawken, 1981), and rats (Fagiolini et al., 1994), but not in V1 of mice (Prusky and Douglas, 2003; Kang et al., 2013b). Our previous studies in Syrian hamsters demonstrated that early visual experience is not necessary for RF refinement in superior colliculus (SC) or V1, but is required to maintain refined adult RFs (Carrasco et al.,

2005; Balmer and Pallas, 2015a). Chronic dark rearing (DR) beyond postnatal day (P) 60 results in expansion of RFs to juvenile size (Carrasco et al., 2005). Light exposure during an early postnatal critical period protects RFs against this later loss of refinement (Carrasco and Pallas, 2006; Balmer and Pallas, 2015a). Thus, in contrast to RF refinement in cats and primates (see Shatz, 1996, for review), development of refined RFs in hamster SC and V1 is independent of sensory experience, and requires vision only for maintenance. These results counter the common view that vision is required for development but not maintenance of visual receptive field properties (see Shatz, 1996, for review). They caution against over-generalization across features and species, and raise the possibility that RF refinement in hamster SC and V1 may occur through a distinct mechanism.

Because RF expansion in SC of DR adults results from a loss of inhibition (Carrasco et al., 2011; Balmer and Pallas, 2015b) we asked whether RF refinement and maintenance might occur through a mechanism other than TrkB directed inhibitory plasticity. We find, however, that TrkB activation during the critical period for RF refinement is necessary and sufficient to maintain refined RFs in SC and V1 of adults. Thus, BDNF-TrkB activity seems to be a common path through which visual experience influences the development and maturation of inhibition in the visual pathway. These findings raise the possibility that manipulating TrkB activity could reactivate plasticity in adults for therapeutic purposes, and could provide insight into the development of disorders that similarly involve the breakdown of mature connectivity stemming from an early developmental error.

2.4 Materials and Methods

2.4.1 Subjects

A total of 137 adult Syrian hamsters (*Mesocricetus auratus*) of both sexes was bred in-house and used in this study (see Table 1). Hamsters provide a valuable model for studying the developing visual system due to their robust and well-characterized visual responses and short gestation time (Pratt and Lisk, 1989). Hamsters were housed in social groups of up to 5 adults per cage in standard rodent cages, with enrichment items including nestlets and chew toys. All animals were provided ad libitum access to food and water 24 hours per day.

Twenty-four adult mice (C57BL/6) of both sexes were bred in-house and used in the visual looming behavioral assay only. Mice are a valuable model for perceptual tasks because they are commonly used in behavior experiments and are widely studied animal model in visual neuroscience.

2.4.2 Surgery

Electrophysiological recordings were made in sedated animals as described previously (Carrasco et al., 2005). In brief, animals were deeply anesthetized with intraperitoneal injections of urethane (2g/kg, split into 3-4 doses). Surgical levels of anesthesia were confirmed via withdrawal reflexes, respiration rate, and muscle tone, with supplemental $\frac{1}{4}$ doses of urethane given as needed. Preoperative doses of atropine (0.05 mg/kg) were administered after the onset of anesthesia to stabilize breathing and reduce secretions in the respiratory tract. A single injection of dexamethasone (1mg/kg) was used as a prophylactic anti-inflammatory. The surgical site was then shaved and cleaned with 70% ethanol, and the head was stabilized with a bite-bar restraint. A midline incision was made in the scalp to expose the skull, followed by an approximately 5mm bilateral craniotomy extending from bregma to lambda, and retraction of the

meninges. The cortex and hippocampus were aspirated unilaterally to expose the underlying SC. Removal of cortex has no observable effect on SC neuron RF properties in hamsters, except for impairments in cortically-mediated direction tuning (Chalupa, 1981; Ahmadlou et al., 2017).

2.4.3 Experimental design and statistical analysis

Light treatment groups Normally reared hamsters or mice were housed in a 12/12 hour, reversed light-dark cycle. DR animals were housed in a darkroom, within which were several light-tight housing cabinets. Pregnant dams of DR subjects were transferred into DR housing approximately 3 days before parturition. During drug administration and for general husbandry purposes, they were briefly exposed to dim red light at a wavelength not visible to Syrian hamsters (Huhman and Albers, 1994).

To test the effect of TrkB receptor blockade on RF maintenance, strobe light exposure was used rather than a 12/12 light cycle because of the likelihood that the injected antagonist would not be effective throughout the 12-hour daily light exposure. Strobe-exposed animals were placed in a small enclosure containing a light flashing at approximately 25 Hz for 5 hours a day on each day of the critical period (7 days total). The timing of strobe exposure overlaps the 6 hour effective dose curve of the TrkB antagonist (Cazorla et al., 2011). This method exposed test subjects to a total duration of light exposure similar to the amount that was sufficient to maintain RF refinement in SC (Carrasco et al., 2005).

Drug treatment groups In order to test the hypothesis that TrkB activation is necessary and/or sufficient for adult maintenance of RF refinement, all animals were administered a daily injection of either a TrkB agonist (Andero et al., 2011), a TrkB antagonist (Mui et al., 2018), or vehicle during the critical period for RF maturation in SC (P33-40) under dim red light conditions (Carrasco et al., 2005). Specifically, treatment consisted of an intraperitoneal

injection of either the TrkB agonist 7,8-Dihydroxyflavone (7,8-DHF) (98% Sigma Aldrich CAS#: 38183-03-8) (10mg/kg) or the antagonist ANA-12 (Sigma Aldrich #SML0209) 0.15g/ml, made fresh daily, dissolved in diluted dimethylsulfoxide (60% DMSO in DI water), or DMSO alone as a negative control. Animals were weighed prior to each daily injection to ensure that the 1 mg/kg dose of drug or vehicle remained consistent throughout the treatment phase.

Statistical analysis A Student's *t*-test or a One-Way Analysis of Variance (ANOVA), followed by post-hoc Bonferroni tests were used to compare parametric data with equal variance between groups and a normally distributed data set. Descriptive statistics for these analyses are provided as mean \pm standard error of the mean (SEM). For data not meeting these criteria, a Mann-Whitney rank sum test or a Kruskal-Wallis One-way ANOVA on ranks was used, followed by a Dunn's post hoc test, with data presented as median \pm interquartile range (IQR).

2.4.4 Western blotting

Animals were euthanized with a sodium pentobarbital-and phenytoin sodium-containing mixture (Euthasol >150 mg/kg IP). Brains were immediately extracted and flash frozen in cold 2-methylbutane on dry ice, then stored at -80°C or immediately dissected for preparation of lysates. Individual left and right tecta were excised and lysed in RIPA buffer (150mM NaCl, 150mM Tris, 1% NP-40, 0.1% SDS, 0.5% sodium deoxycholate) containing 2% Halt protease inhibitor (ThermoFisher Scientific). Proteins were visualized using SuperSignal West Pico Chemiluminescent Substrate kits (Life Technologies) and imaged on an ImageQuant LAS4000 mini imaging system (GE Healthcare Life Sciences), or IRdye fluorescent secondaries (Li-Cor), imaged on an Odyssey CLx fluorescent imaging system (Li-Cor). Protein levels were quantified as the optical density of the phosphorylated TrkB proteins relative to the optical density of total TrkB protein using ImageJ. No difference was detected between the two imaging methods using

identical membranes, thus the data were combined. To assess the effectiveness of the TrkB agonist and antagonist, 33 animals received the drug doses IP, and then either remained in their DR habitat or were exposed to strobe conditions for 2 hours, followed by euthanasia and tissue harvest. Rabbit anti-pTrkB (Y817) (1:1000, Abcam Cat # ab81288), and rabbit anti-pan (total) TrkB (80G2, 1:500, Cell Signaling Technologies Cat# 4607) were used to confirm that the drugs were having the expected effect on TrkB phosphorylation in *in vivo*. The Y817 phosphorylation site was chosen because it is a BDNF phosphorylation site (Liu et al., 2014) and its phosphorylation is a reliable marker for calcium release (Hubbard and Miller, 2007). Phosphorylation of Y817 also activates protein kinase C (PKC), which is associated with activity dependent synaptogenesis in visual cortical development (Zhang et al., 2005). Negative controls included lanes with primary antibody but no protein to confirm specificity of the bands identified at the targeted molecular weight.

2.4.5 Assessment of pre- and post-synaptic inhibitory signaling strength

To characterize and compare treatment dependent changes in inhibitory signaling in adulthood we examined levels of GAD-65 and GABA_AR α 1 protein using antibodies (mouse anti-GAD-65 1:10 (Developmental Studies Hybridoma Bank-University of Iowa GAD-6), and rabbit anti-GABA_AR α 1 1:1000 (Abcam ab33299)). Negative controls included lanes without protein and lanes without primary antibody.

2.4.6 Electrophysiology

Single unit extracellular recordings were obtained with Teflon coated, glass insulated microelectrodes (Kation Scientific, Catalog: W1011-7, 2-2.3 M Ω). The electrode was positioned perpendicular to the exposed SC, and lowered into the tissue using a Kopf Model 650 micropositioner. All recordings were obtained within 200 μ m of the surface of the SC to ensure

they were made from the superficial, retino-recipient layers. Electrical signals were amplified, filtered (10,000x; 0.5-3kHz; Bak Electronics A-1), and digitized at 20 kHz using Spike2 software and CED hardware (Micro 1401-2; Cambridge Electronic Design).

2.4.7 Visual stimulus presentation

In order to measure RF size, we used a visual stimulus presented on a CRT monitor (60Hz refresh rate) positioned 40 cm from the left eye. The monitor was maintained at its highest contrast and brightness settings for each experiment. Visual stimulus generation was accomplished using custom MATLAB (Mathworks) software with the PsychToolBox-3 application. The visual stimulus consisted of a bright white square traveling from dorsal to ventral visual field at $14^\circ/s$ across a black background. The stimulus size was 1 degree in diameter and each vertical traverse shifted 2° along the x axis of the monitor after each presentation, with a 3 second inter-stimulus interval, as in (Balmer and Pallas, 2015a).

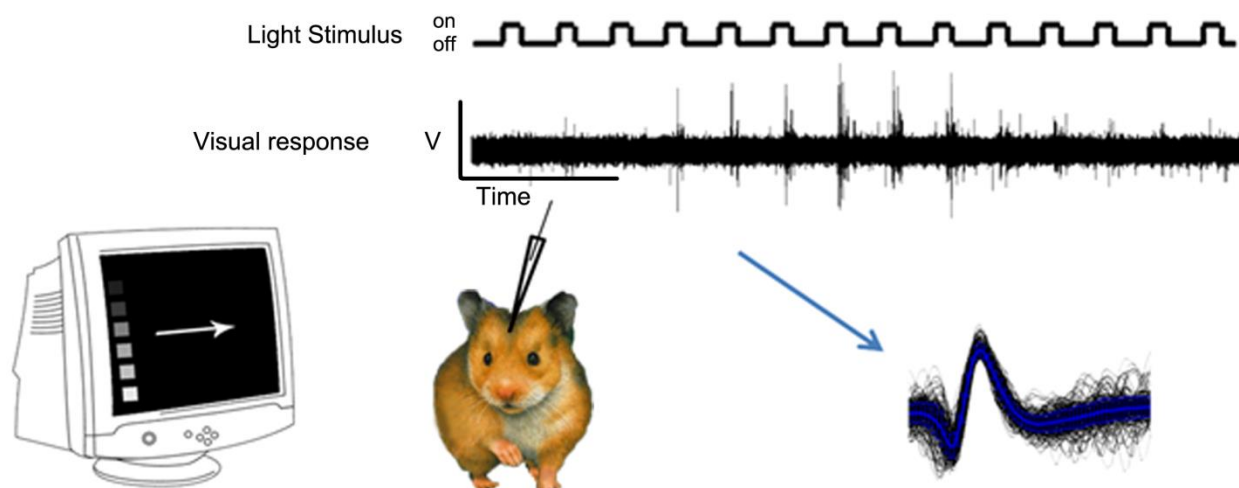


Figure 2.1: Graphical description of experimental procedure for measuring visual RF sizes with *in vivo*, extracellular, single-unit recordings of stimulus-evoked action potentials in SC.

2.4.8 Analysis of RFs

Spike2 software (Cambridge Electronic Design) was used for offline spike sorting of single units (approximately four unique visually responsive neurons were isolated per recording site). Analysis of RF size was completed by a researcher blind to treatment group. Receptive field diameter along the azimuthal axis was measured by plotting the visual field location from which spiking responses were produced as the stimulus vertically traversed the monitor, from nasal to temporal visual field. A uniform fraction of the peak response (20%) was defined as the minimum stimulus-evoked response threshold, as in a previous study (Balmer and Pallas, 2015a). Responses were normalized by setting the peak response of each single unit to 1.0 to account for differences in response strength between individual units. RF size data were compared between treatment groups to quantify the effect of TrkB manipulation vs. vehicle treatment. Data for LR Control and DR Control groups were taken from our previously published study, using the same methods (Carrasco et al., 2005).

2.4.9 Looming response task

An open-top box with dimensions of 58.7cm long x 42.9cm wide and 32.4cm in height was used to test the fear reflex to an expanding spot approaching from above. The test subjects were light and dark reared Syrian hamsters and C57BL/6J mice, aged >P90, housed either in 12h:12h light:dark cycle or in 24h dark. Five trials were conducted under white light, in the animals' subjective daytime between the hours of 1900-2200. Both groups were exposed to white light for less than 90 minutes per trial. Alcohol (70%) was used to clean the apparatus before and between each trial, to eliminate olfactory cues. A plastic cup was spray painted black and offered as a hiding chamber. Each subject was placed in the center of the apparatus with the white monitor screen above and given at least 10 minutes for acclimation. The visual stimuli

were programmed and displayed using the Psychtoolbox module for MATLAB. A spherical, black, looming stimulus on a white background was initiated once the subject was out of the hiding chamber and in the center of the arena. The stimulus expanded from 3.5 degrees of visual angle to 56.5 degrees in 2.35 seconds, remained at that size for 250ms, and then restarted the sequence with a 250ms delay. The fear response was considered positive if the subject either froze or fled into the cup within 5 seconds of the stimulus initiation. The fear response was considered negative if the subject did not demonstrate any freezing or fleeing behavior.

2.4.10 Visual water maze task

A two-alternative, forced-choice visual discrimination task was used to assess the spatial acuity of Syrian hamsters across all treatment groups. The task consisted of a trapezoidal shaped Y maze half- submerged in a pool with 15cm of tepid (22°C) water. A hidden escape platform that was submerged in one of the two distal arms of the maze was separated by an opaque divider 40cm in length, with the far end of the divider marking the decision line. Identical monitors (Dell Model 1707FPt) placed side by side and above the distal ends of the maze displayed either a gray screen or a sinusoidal grating of vertical black and white bars. The maximum detectable number of grating cycles (cycles per degree – cpd) that occurred throughout the span of a single visual degree for the subjects was calculated and used as a measure of visual acuity. Screen reflections on the surface of the water hid the platform when viewed from water level. Hamsters were trained to escape from the Y maze by swimming toward the screen displaying the gratings, where the hidden platform was located. Visual acuity was determined by increasing the number of grating cycles across the screen (adding 1 complete cycle for each progressive set of trials). The escape platform location was randomly determined before each set of trials. When an incorrect choice was made, the animal would be assayed over several more trials to determine an

overall success rate at that cpd. If the animal fell below a 70% success rate then its preliminary visual acuity was determined to be the total cpd of the previous trial set. The final visual acuity value for each animal was progressively narrowed down over the course of several days and approximately 60 trials per animal.

2.4.11 Data sharing information

Intellectual property rights are set by Georgia State University Policy No. GSU: 4.00.08. Data will be embargoed only until publication, unless the University requests a delay in public dissemination if necessary to permit the University to secure protection for Intellectual Property disclosed to it by the PI. After publication, we are willing to share any of the data used to generate our manuscripts as long as the PI and members of the Pallas lab involved in generating the data and the funding sources receive proper attribution.

2.5 Results

The developmental transition from plastic to stable receptive field properties maintains the activity driven changes that occur in early life. Early visual experience is required for refined RFs to be stabilized and thus maintained into adulthood (Carrasco et al., 2005), but it remains unclear what molecular changes are responsible. BDNF protects against degradation of visual acuity in visual cortex of dark reared mice (Gianfranceschi et al., 2003), and we examined whether BDNF-TrkB signaling might also be protective of acuity in SC of dark reared hamsters, in which case it may be a general mechanism through which sensory experience has its maturational effects across species and brain area. Alternatively, adult maintenance of RF refinement in Syrian hamsters may occur through a different signaling pathway.

2.5.1 7,8-DHF and ANA-12 are both effective modulators of TrkB receptors throughout the visual midbrain

In the study on the effects of visual deprivation on visual cortical development of mice mentioned above (Gianfranceschi et al., 2003), a genetic approach was used for constitutive over-expression of BDNF. We asked a more time-limited question- whether increasing signaling through the TrkB BDNF receptor only during an early critical period would have a similar effect. To accomplish this, we used a pharmacological approach that allowed us to control the timing of TrkB manipulation. We reasoned that if increased TrkB signaling that is limited to the critical period could rescue receptive field properties from the effects of visual deprivation, it would suggest that a common mechanism exists for stabilizing inhibitory synapses across different visual brain areas and species, despite the differences in timing. Systemic injection of the isoflavone 7,8-DHF as a TrkB receptor agonist (Andero et al., 2011; Liu et al., 2014), and ANA-12 as an antagonist (Lawson et al., 2014; Ren et al., 2015) have been used to manipulate TrkB activation in previous studies. In order to determine whether we could use these drugs to achieve a level of TrkB activation during the critical period that would be comparable to that provided by light exposure, we assayed their ability to phosphorylate and dephosphorylate TrkB receptors at the same site that is phosphorylated by light exposure and BDNF binding (Y817) (Poo, 2001; Hubbard and Miller, 2007; Liu et al., 2014). Test subjects from each treatment group (7,8-DHF + DR, n=9; Strobe + ANA-12, n=5; Strobe alone, n=7; Vehicle + DR, n=11) were euthanized 3 hours after receiving treatment, and the brains were collected for processing.. We then used Western blotting to measure the amount of activated (pTrkB) relative to total TrkB from V1, SC, and hippocampus (as a non-retinorecipient control region). We found that the pharmacological manipulations intended to stimulate TrkB receptors were working as intended, in that

immunoblotting with antibodies against phosphorylated (activated) and total TrkB receptors revealed strong, treatment-induced increases in TrkB phosphorylation at Y817 throughout the brain (**Figure 2.2**). In all three areas 7,8-DHF had a robust effect on increasing TrkB phosphorylation in DR subjects well beyond that of the Vehicle + DR injection group; SC ($F(3,24) = 12.503$, $p < 0.001$, ANOVA) V1 ($F(3,12) = 24.757$ $p < 0.001$, ANOVA), hippocampus ($F(3,12) = 6.070$ $p = 0.009$, ANOVA). Visual experience (strobe) also induced increases in pTrkB in both visual brain areas compared to vehicle: SC (0.523 ± 0.0916 , $p = 0.046$, $n=5$), V1 (0.529 ± 0.0812 , $p = 0.004$, $n=4$), but not in hippocampus, as expected for a non-visual area. Conversely, treatment with the TrkB antagonist ANA-12 + strobe reduced pTrkB levels in relation to total TrkB in both SC (0.132 ± 0.243 , $p = 0.034$ $n=3$) and V1 (0.098 ± 0.0265 $p < 0.001$ $n=4$). These findings support our claim that pharmacological activation of TrkB agonists can modulate TrkB activity in hamster SC, similar to short, stroboscopic light treatments, whereas antagonist treatment can reduce TrkB activation, mimicking visual deprivation.

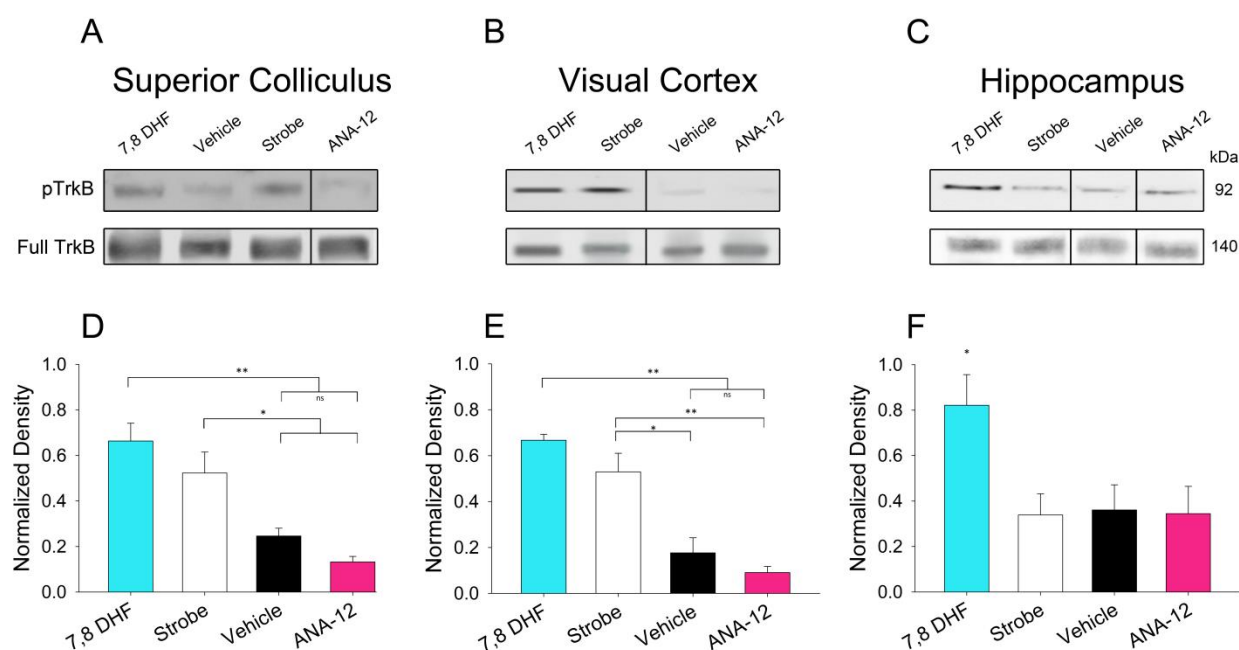


Figure 2.2: Drug treatments were effective at modulating TrkB activity in SC, V1, and hippocampus.

7,8-DHF administration from P33–P40 increased TrkB receptor activation, and ANA-12 treatment blocked TrkB activation, in all brain areas assayed. *A–C*, Example blots of treatment groups generated using 20 μ g of protein per lane. All presented lanes are from the same gels, with nonadjacent lanes revealed by vertical lines between them. *D–F*, Densitometric analyses of Western blots generated from SC (*D*), V1 (*E*), or hippocampus (*F*) lysates prepared from juvenile hamsters (\sim P33) receiving the TrkB receptor agonist (7,8-DHF), visual experience (strobe light for 1 h), strobe light + the TrkB antagonist ANA-12, or vehicle injection revealed differences in activation levels of TrkB receptors between groups. Agonist and strobe light exposure greatly increased levels of phosphorylated (p)TrkB in SC compared with vehicle. Analysis of ANA-12 treatment on TrkB phosphorylation during 1 h of strobe light exposure revealed that the antagonist is effective in preventing visual experience-evoked TrkB activation. The density of the anti-pTrkB (Y817) band is normalized to the anti-total TrkB (80G2) protein band to measure differences in TrkB activity. Data are mean \pm SEM. * $p < 0.05$, ** $p < 0.01$, ns, not significant.

2.5.2 Elevating TrkB receptor phosphorylation levels during the critical period maintains SC receptive field refinement into adulthood

In SC and V1, refinement of RFs during postnatal development occurs independently of visual experience, but maintaining refined RF size into adulthood requires visual experience during an early critical period (Carrasco et al., 2005; Balmer and Pallas, 2015a). Because genetically increasing BDNF expression throughout life rescues RF size in dark reared visual cortex of mice (Gianfranceschi et al., 2003), we reasoned that early BDNF signaling might also be involved in RF maintenance in adult superior colliculus. To investigate whether TrkB

activation during the critical period for RF plasticity has the same effect on RF size as visual experience, we pharmacologically manipulated TrkB activation during the critical period and measured RF sizes in adult superior colliculus (>P90). Data for LR Control and DR Control groups were taken from our previously published study, using the same methods (Carrasco et al., 2005). Our approach was to dark rear hamsters from <P0 to >P90 and provide daily treatment with the TrkB agonist 7,8-DHF throughout the critical period (P33-P40). As predicted, DR hamsters that were treated with the agonist maintained a significantly smaller RF size ($12^\circ \pm 6^\circ$, $n = 92$) compared to vehicle injected control animals ($18^\circ \pm 4^\circ$, $p < 0.05$, $n = 84$) ($H(3) = 120.118$, $p = < 0.001$, Kruskal Wallis One-Way ANOVA on Ranks) (**Figure 2.3**). Importantly, these are measurements of single unit RF sizes, and not overlapping, adjacent RFs that might be measured from multiunit extracellular recordings. These results support the hypothesis that TrkB activation during the critical period is sufficient to maintain RF refinement in SC into adulthood.

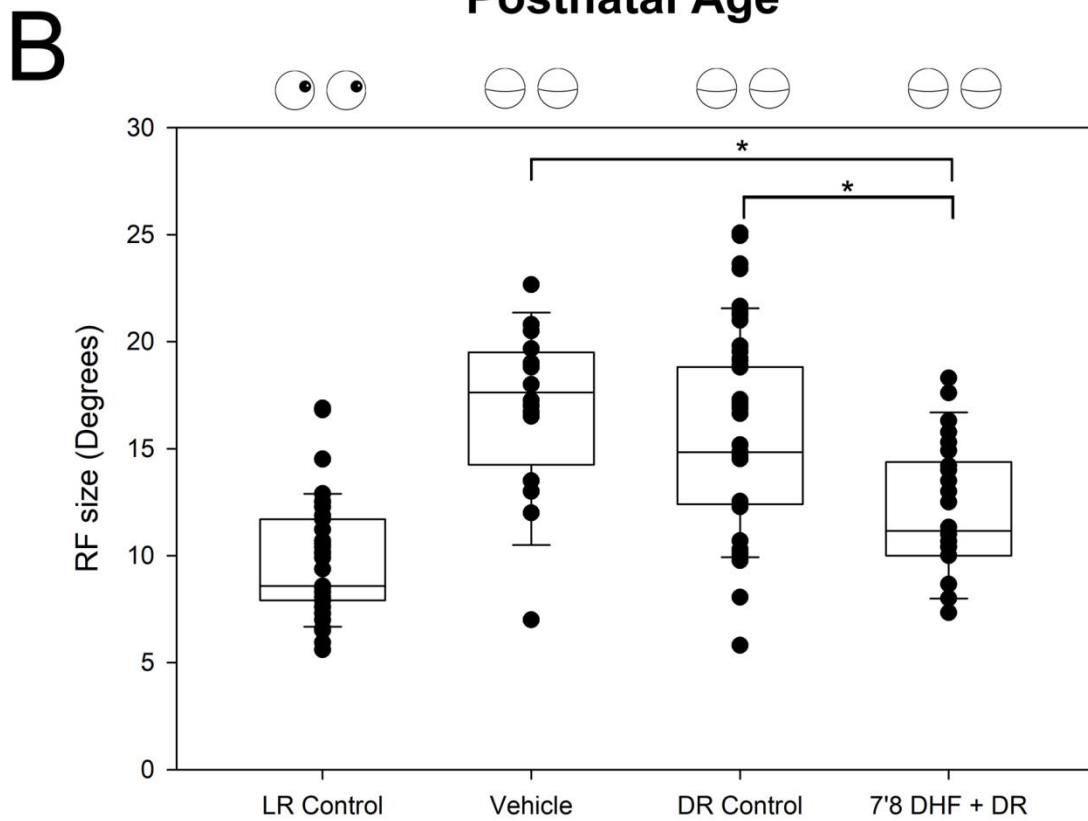
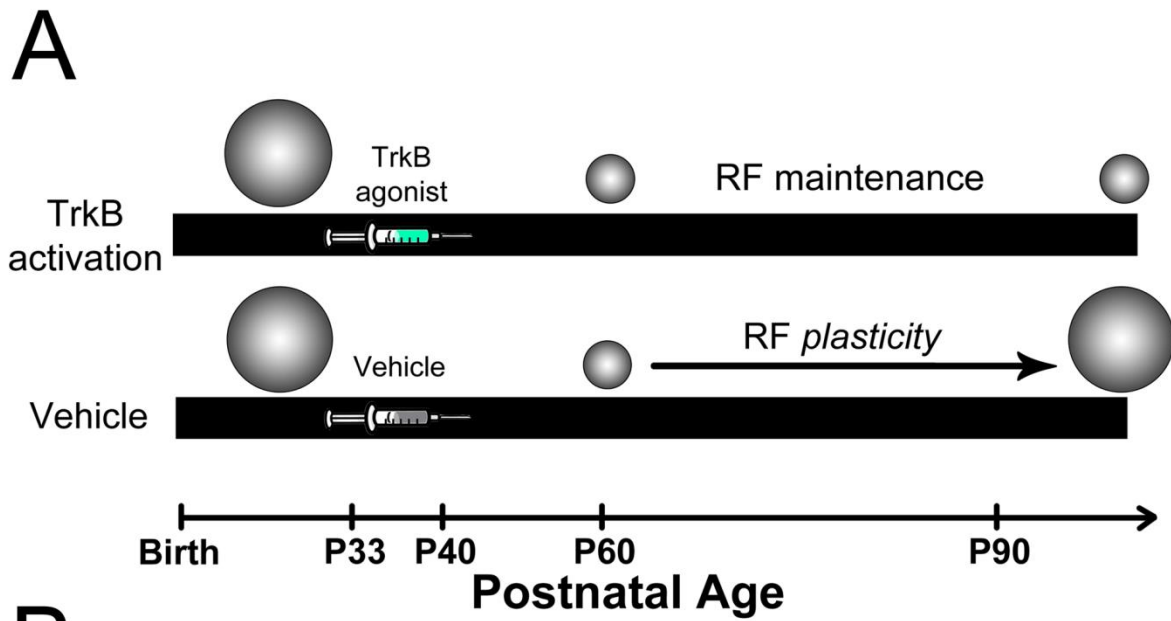


Figure 2.3: TrkB activation during the critical period maintains RF refinement into late (>P90) adulthood.

A, Experimental design and summary of findings. B, RF sizes for each experimental group measured in visual degrees and plotted as individual data points. LR and DR control data are

from *Carrasco et al. (2005)*. Open pair of eyes across the top of graph indicates the group was given visual experience. Closed eyes indicate group was DR throughout development. Data are median \pm IQR. * $p < 0.05$.

2.5.3 Decreasing TrkB phosphorylation levels during the critical period prevents maintenance of SC receptive field refinement into adulthood

Next, we tested whether TrkB activation is a requirement for maintenance of refined RFs. Our approach was to use the TrkB antagonist ANA-12 to block the light-induced phosphorylation of TrkB receptors that occurs during visual experience. ANA-12 was administered during a stroboscopic presentation of light for 5 hr/day throughout the critical period (P33-P40), followed by return to the dark room until adulthood ($>P90$). This stroboscopic light treatment was sufficient to maintain RF refinement in SC into adulthood (**Figure 2.4**). Single-unit recordings from SC neurons in animals receiving the antagonist revealed significantly larger RFs ($20^\circ \pm 4^\circ$ (n=82 neurons)) than in neurons from strobe light treated animals ($12^\circ \pm 4^\circ$ (n=29 neurons)) (**Figure 2.4B**) and interestingly, larger RFs than in vehicle injected, light exposed subjects ($18^\circ \pm 4^\circ$ n = 84)($H(3) = 153.50$, $p = < 0.001$, Kruskal Wallis One-Way ANOVA on Ranks). We further compared the effects of all treatments on adult RF size across different quadrants of the SC and observed no significant differences between strobe, vehicle + DR, or ANA-12 + strobe, suggesting that no regions of the SC are particularly susceptible to DR. Note that the plot includes data from LR Control and DR Control groups in our previously published study (Carrasco et al., 2005). Interestingly, we did observe more refinement in RFs located in the rostral ($10^\circ \pm 2.5^\circ$, n= 21) and medial ($10^\circ \pm 4^\circ$, n=17) quadrants of the SC compared to the caudal ($14^\circ \pm 4^\circ$, n=29) and lateral ($14^\circ \pm 4^\circ$, n= 28)

quadrants (**Figure 2.5**), consistent with recent findings that certain visual stimulus features may be sampled more robustly at different regions of the visual field (El-Danaf and Huberman, 2019). These findings further supports the hypothesis that TrkB activity is responsible for maintenance of RF refinement, because blocking TrkB activity during the critical period resulted in enlarged RFs in adulthood, despite adequate visual experience for maintenance of refined receptive fields.

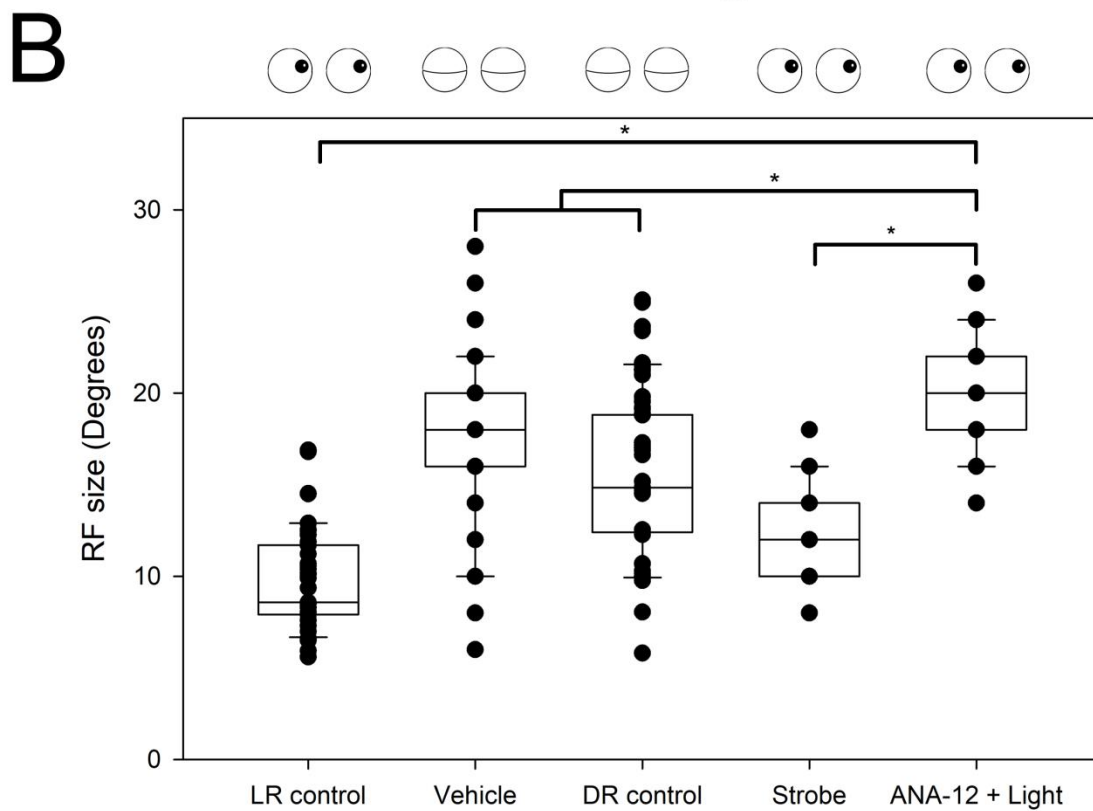
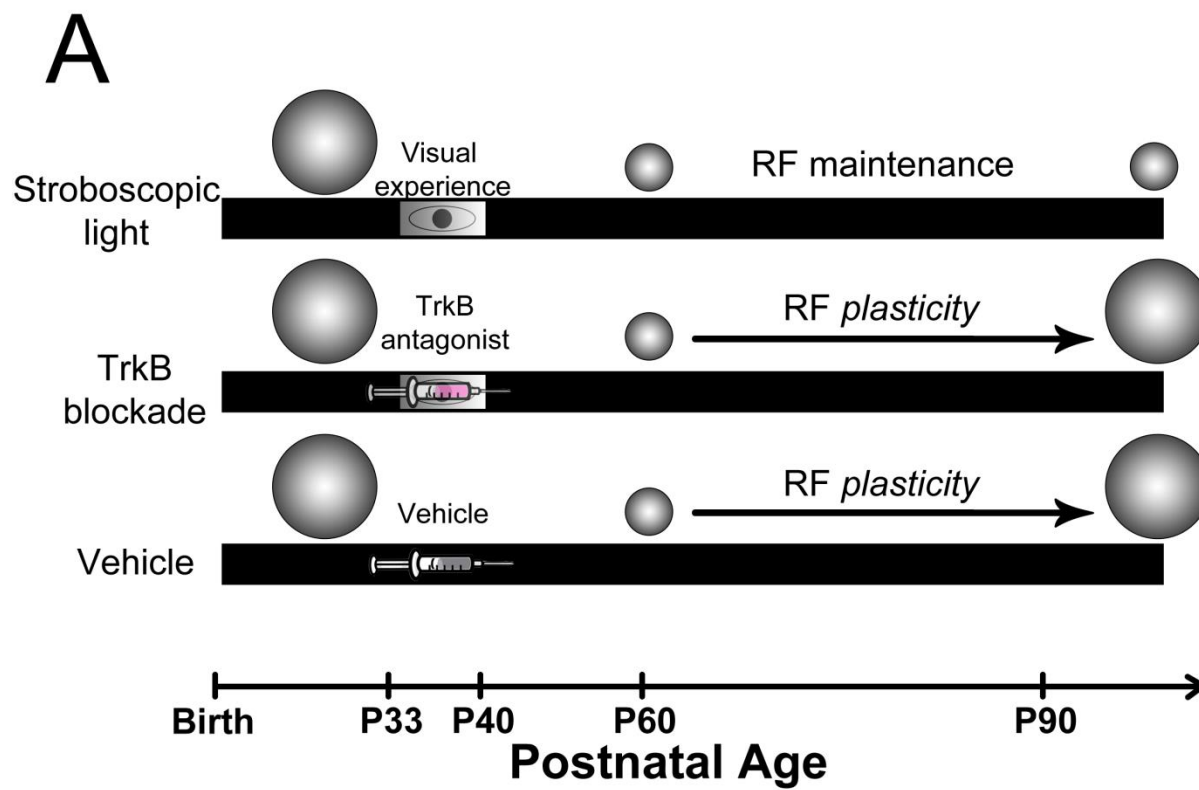


Figure 2.4: TrkB blockade during the critical period blocks the protective effects of visual experience for SC RF refinement in adulthood (>P90).

DR animals were given sufficient stroboscopic visual experience during the critical period to maintain RF refinement in SC, but TrkB blockade during that time period blocked the protective effects of light. **A**, Experimental timeline for treatment and resulting RF changes during development. **B**, RF sizes for each experimental group measured in visual degrees and plotted as individual data points. LR and DR control data are from [Carrasco et al. \(2005\)](#). Symbols are as in [Figure 2.3](#). Data are median \pm IQR. * $p < 0.05$.

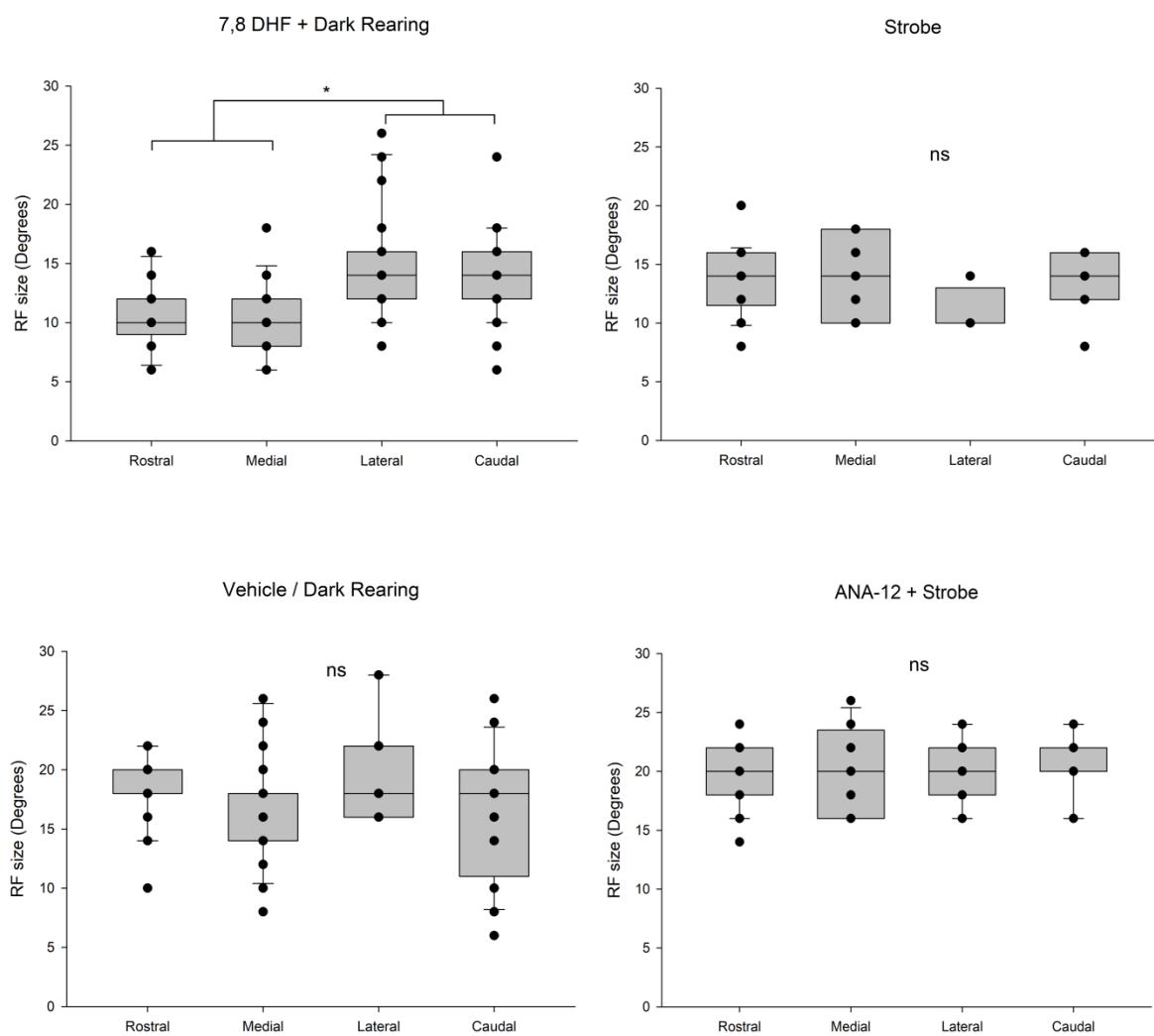


Figure 2.5: Analysis of treatment effect on RF size across quadrants of SC.

In the 7,8-DHF groups, the RFs in SC neurons representing the rostral and medial quadrants of the visual field were smaller than those in the caudal and lateral quadrants. In adult hamsters, these regions receive topographic input from the nasal and dorsal visual fields, respectively. No other treatment elicited a quadrant specific effect on RF size. Data are median \pm IQR. * $p < 0.05$, ns, not significant.

2.5.4 TrkB activity during the critical period preserves RF refinement by maintaining adult levels of inhibition

Results from our previous investigations suggested that loss of inhibition could account for the RF enlargement in adult DR animals (Carrasco et al., 2011; Balmer and Pallas, 2015a). If TrkB is the pathway through which visual deprivation leads to a loss of lateral inhibition in SC and thus enlarged RFs in adulthood, then reduced TrkB activation should result in reduced inhibition. Thus we examined how altering TrkB activation affected GABA and GABA_A receptor levels. Examinations of the GABA precursor enzyme (GAD65) levels and GABA_AR receptor expression levels in TrkB agonist and antagonist-treated hamsters were used to examine any potential changes in adult inhibition. Assays of GAD65 and GABA_A receptor levels allowed us to address if increasing TrkB activity during the critical period in DR hamsters would maintain adult levels of lateral inhibition in SC in the same manner as visual experience, or if TrkB activity is affecting RF refinement in SC through a different mechanism.

We measured adult (>P90) levels of GAD65 and GABA_AR α 1 receptor subunit protein in drug-treated and control animals using Western blotting. Agonist (7,8-DHF/DR) treated animals had higher relative cytoplasmic GAD65 expression (0.216 ± 0.006 , $n = 7$ animals) compared to vehicle /DR treated (0.104 ± 0.0121 , $n = 5$), and antagonist (ANA-12/strobe) treated hamsters (0.085 ± 0.0092 , $n=4$) ($F(4,28) = 102.747$, $p < 0.001$, One-Way ANOVA). Normally reared and

DR control groups performed as expected, with normally reared hamsters having much higher GAD65 expression compared to DR hamsters (Normal: 0.242 ± 0.0057 , $n = 6$; DR: 0.0737 ± 0.0048 , $n=4$; One-Way ANOVA, $p < 0.001$) (**Figure 2.6A**). In contrast, drug treatment had no effect on GABA_AR $\alpha 1$ expression ($p = 0.97$) (**Figure 2.6B**). Presynaptic GAD65 expression was reduced in groups in which RFs had become unrefined (Vehicle, DR, ANA-12/Strobe), whereas post-synaptic receptor function was not affected. These results suggest that visual experience and TrkB activity are not functioning via unique signaling pathways.

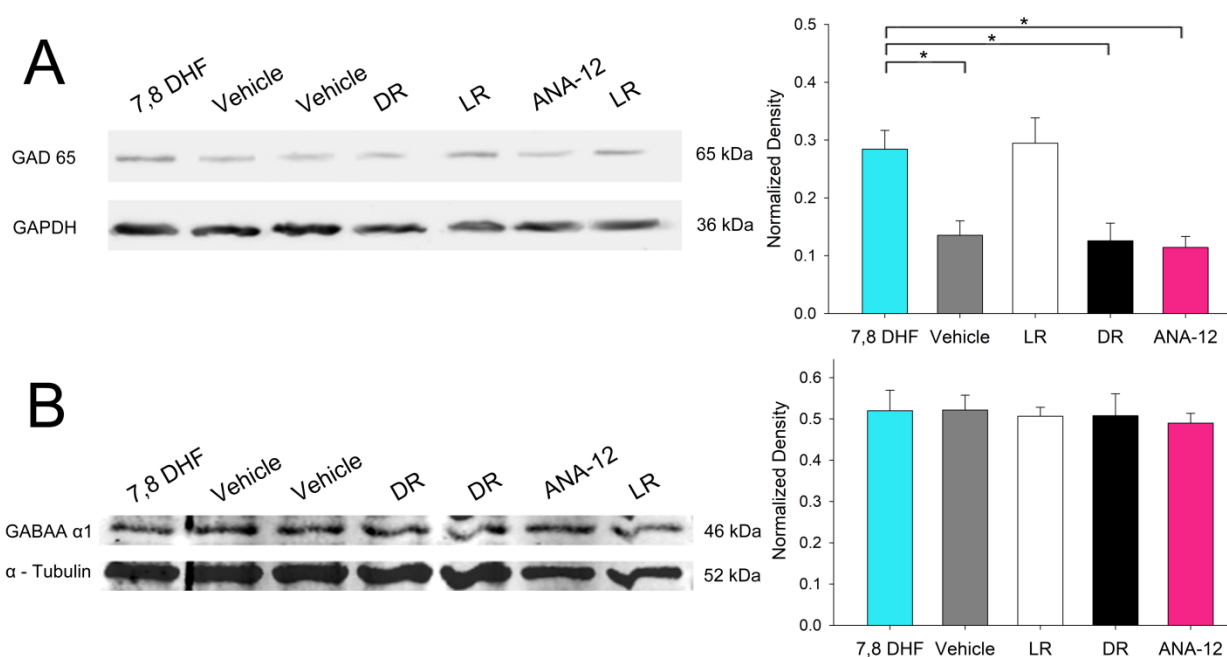


Figure 2.6: Early TrkB expression is both necessary and sufficient to maintain increased presynaptic inhibition in adult SC.

A, Adult GAD65 expression levels were maintained in TrkB agonist-injected animals but decreased in DR, vehicle, and ANA-12-injected animals. **B**, GABA_AR $\alpha 1$ expression remained constant across all treatment groups and rearing conditions. Data are mean relative optical density \pm SEM. $*p < 0.001$.

2.5.5 *Dark rearing impairs fear responses to looming visual stimuli*

RF refinement is critical for the development of visual acuity and environmental awareness. DR animals have a number of visual deficits in cortex such as poorer visual acuity and broader orientation and direction tuning (Fagiolini et al., 1994), but deficits in SC have rarely been characterized. In rodents, the retino-SC pathway is arguably more relevant to visual behavior than the geniculocortical pathway (Sherman and Spear, 1982; Li et al., 2015; Beltramo and Scanziani, 2019), especially compared to predators. We hypothesized that refined RFs are necessary for SC dependent visual behaviors to function in adulthood, and predicted that groups with enlarged RF's (DR/Vehicle, ANA-12/Strobe) would have impaired task performance. We tested this hypothesis in adult hamsters by examining differences in fear responses (escape or freezing behavior; see Methods) to visual looming stimuli (**Figure 2.7A, B**), an SC dependent behavior (Zhao et al., 2014; Shang et al., 2018) that is dependent on input from retinal W3 cells (Zhang et al., 2012). We found that DR ($40\% \pm 6\%$, $n=8$), vehicle ($23\% \pm 8\%$, $n=7$), and ANA-12/strobe ($26\% \pm 4\%$, $n=7$) treated hamsters were less likely to respond to overhead looming stimuli than normally reared ($78\% \pm 6\%$, $n=8$), or 7,8-DHF treated ($70\% \pm 4\%$, $n=6$) hamsters (**Figure 2.7C, E**) ($F(4, 35) = 17.73$, $p < 0.001$, One-way ANOVA).. Dark rearing/larger RFs had a particularly robust effect on the escape (“flight” to shelter) behavior, with very few occurrences of flight in groups in which RFs have expanded in adulthood (**Figure 2.7C**). These data suggest that the failure to maintain RF refinement in adult SC has a negative impact on instinctual fear responses to a looming visual object.

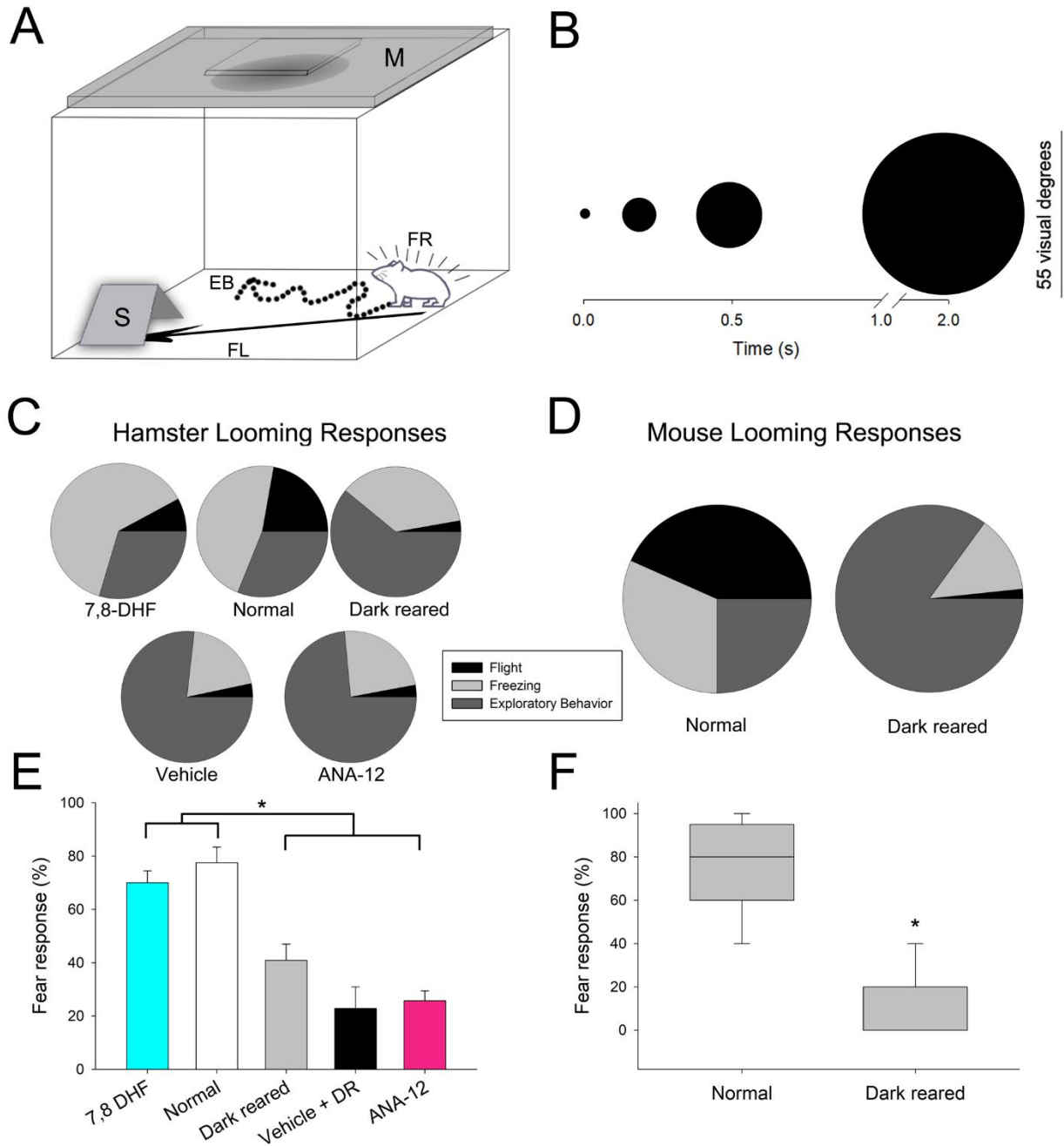


Figure 2.7: DR and subsequent enlargement of RF size in SC reduces fear responses to looming stimuli in hamsters and mice.

A, Schematic of apparatus. A box with a monitor (M) suspended above it projecting the looming stimulus, and a shelter (S) placed at the far end. Animals responded to looming stimuli either by fleeing (FL) into the shelter or freezing (FR) in place. Unresponsive animals continued exploratory behavior (EB). **B**, Expansion of the looming stimulus from the start of a cycle to the

end (~2 s). **C, D**, Occurrences of each response type to looming stimuli per animal in each experiment group for 5 s after stimulus presentation in hamsters (**C**) and mice (**D**). Responses were determined on an ascending scale from exploratory behavior (EB) < freezing < flight, with only the highest observed behavior reported for each trial. **E, F**, The frequency of an escape response (freezing/flight) to looming stimuli compared between normally reared and DR groups in hamsters (**E**) and mice (**F**). Data are mean fear response \pm SEM (**E**) and median \pm IQR (**F**). $*p < 0.05$.

It is important to address the possibility of species-specific responses to light deprivation. Because hamsters are a crepuscular species (Apfelbach and Wester, 1977) and as such encounter their environment in both light and darkness, the effects of light deprivation may not be as detrimental as on a nocturnal species that is less reliant on vision for survival. To test this hypothesis, we carried out the same visual perceptual test on mice that had been normally reared or DR. We found that the effect of DR on the frequency of fear responses to looming stimuli was similar between mice and hamsters. As with DR hamsters, DR mice were less likely to respond to overhead looming stimuli ($20\% \pm 20\%$, $n=12$) than normally reared mice ($80\% \pm 30\%$, $n=12$) ($T=220$, $n(\text{small})=12$, $n(\text{big})=12$, $p<0.001$ Mann-Whitney Rank Sum Test,). Surprisingly, the decrease in fear responses in DR mice was even greater than the decrease in DR hamsters (**Figure 2.7D, F**), contrary to what might be predicted in a nocturnal species like mice. These data suggest that both hamsters and mice are susceptible to DR induced disruptions of visual perception in SC. They also support our contention that RF size refinement is an important event in visual development and could have a detrimental effect on behaviors that are important for survival.

2.5.6 TrkB activity during the critical period for RF refinement is both necessary and sufficient for visual acuity improvements to persist into adulthood

In rats, cortex-dependent visual acuity at eye opening, as assessed by visual evoked potentials, is less than half that in adulthood (Fagiolini et al., 1994). In both SC and V1 of hamsters, chronic DR impairs the stability of the refined RFs, resulting in RF expansion in adulthood (Carrasco et al., 2005; Balmer and Pallas, 2015a) We hypothesized that TrkB activity during the critical period for RF refinement would be both necessary and sufficient for adult visual acuity to be preserved. To test this hypothesis, we compared the proficiency of hamsters in performing a spatial discrimination task in adulthood across treatment groups (7,8-DHF/DR, ANA-12/Strobe, Strobe, DR, and Vehicle/DR) (**Figure 2.8A,B**). We found that visual acuity was similar between strobe treated ($0.695 \text{ cpd} \pm 0.01$, $n=9$), and 7,8-DHF/DR treated ($0.704 \text{ cpd} \pm 0.01$, $n=6$) hamsters, but was reduced in Vehicle/DR ($0.473 \text{ cpd} \pm 0.01$, $n=7$), DR (0.481 ± 0.01 , $n=11$), and ANA-12/Strobe treated hamsters (0.516 ± 0.01 , $n=7$, $F(4,35) = 42.31$, $p < 0.001$, One-Way ANOVA) (**Figure 2.8C,D**). These results demonstrate that TrkB activity during the critical period for RF refinement is both necessary and sufficient for high visual acuity in adulthood, and that RF size refinement is important for overall visual acuity and for survival behaviors such as the looming response.

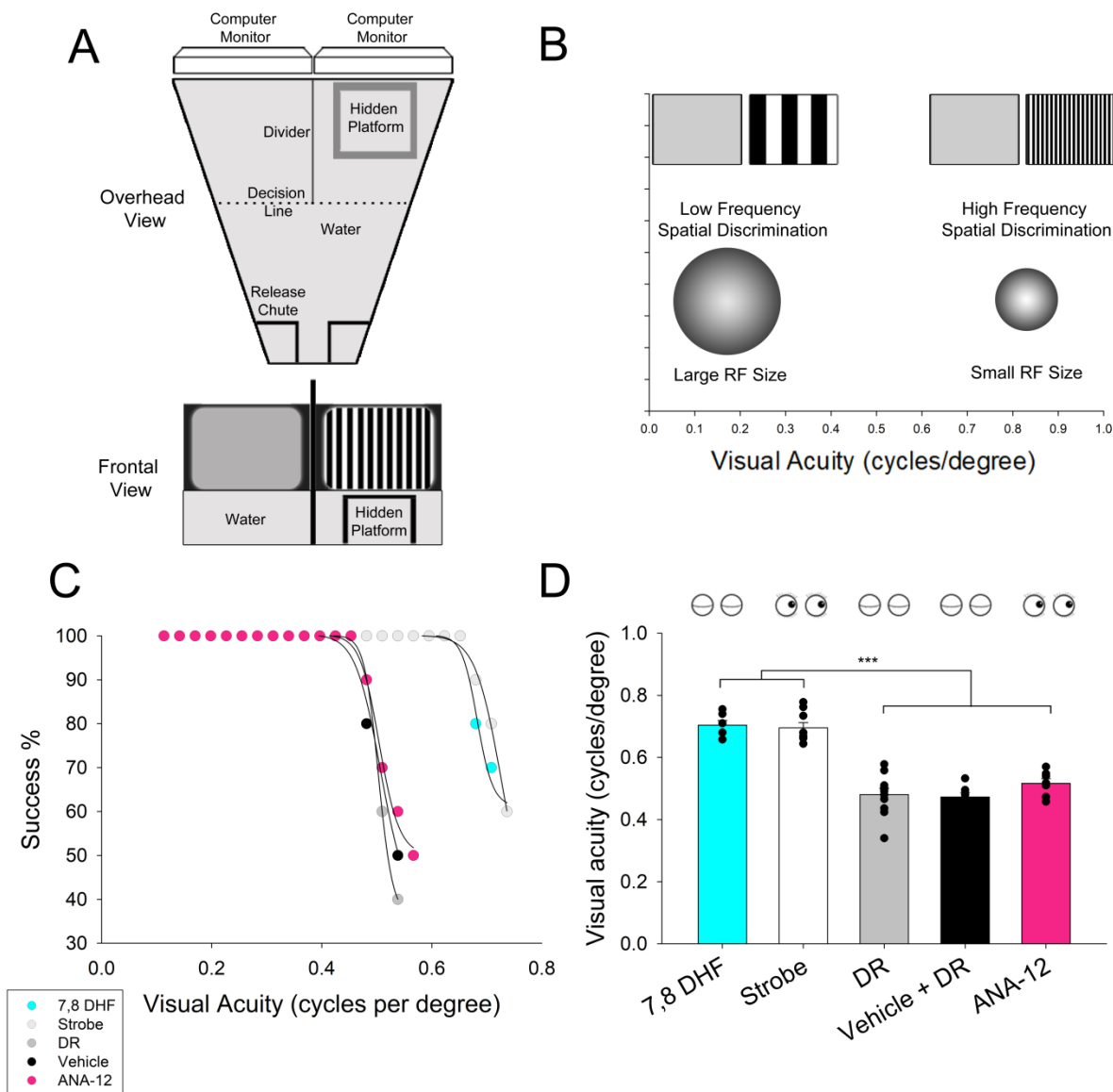


Figure 2.8: *TrkB* activity during the critical period for RF refinement maintains adult levels of visual acuity.

A, Schematic of apparatus from two vantage points. A trapezoidal Y maze filled with 15 cm of water was used in a forced choice behavioral assay. Monitors placed above each arm displayed either a vertically oriented sine-wave grating to indicate the location of the escape platform or a gray screen, in random order. **B**, Progression of trials testing visual discrimination against increasing frequencies of sine-wave gratings. Animals with larger RFs are expected to have poorer visual discrimination ability. **C**, Acuity performance curves were applied to each

treatment group. Each point represents the average success rate at the indicated spatial frequency. Acuity was determined by identifying the point where the curve crossed the horizontal line indicating a 70% success rate. **D**, Comparison of visual acuities in cycles per degree across all treatment groups. Symbols are as in [Figure 2.3](#). Data are mean \pm SEM. *** $p < 0.001$.

Together, these results demonstrate that TrkB activation can substitute for visual experience during the critical period of RF plasticity, and they support the hypothesis that TrkB activation is both necessary and sufficient for the maintenance of RF refinement in SC (**Fig. 9**). Our results also provide evidence that this early increase in TrkB expression reduces presynaptic GAD65 expression in adult SC. In addition, RF refinement in SC is important for visual behavior, in that larger RFs result in impaired responsivity to looming visual stimuli, and poorer discrimination of spatial gratings.

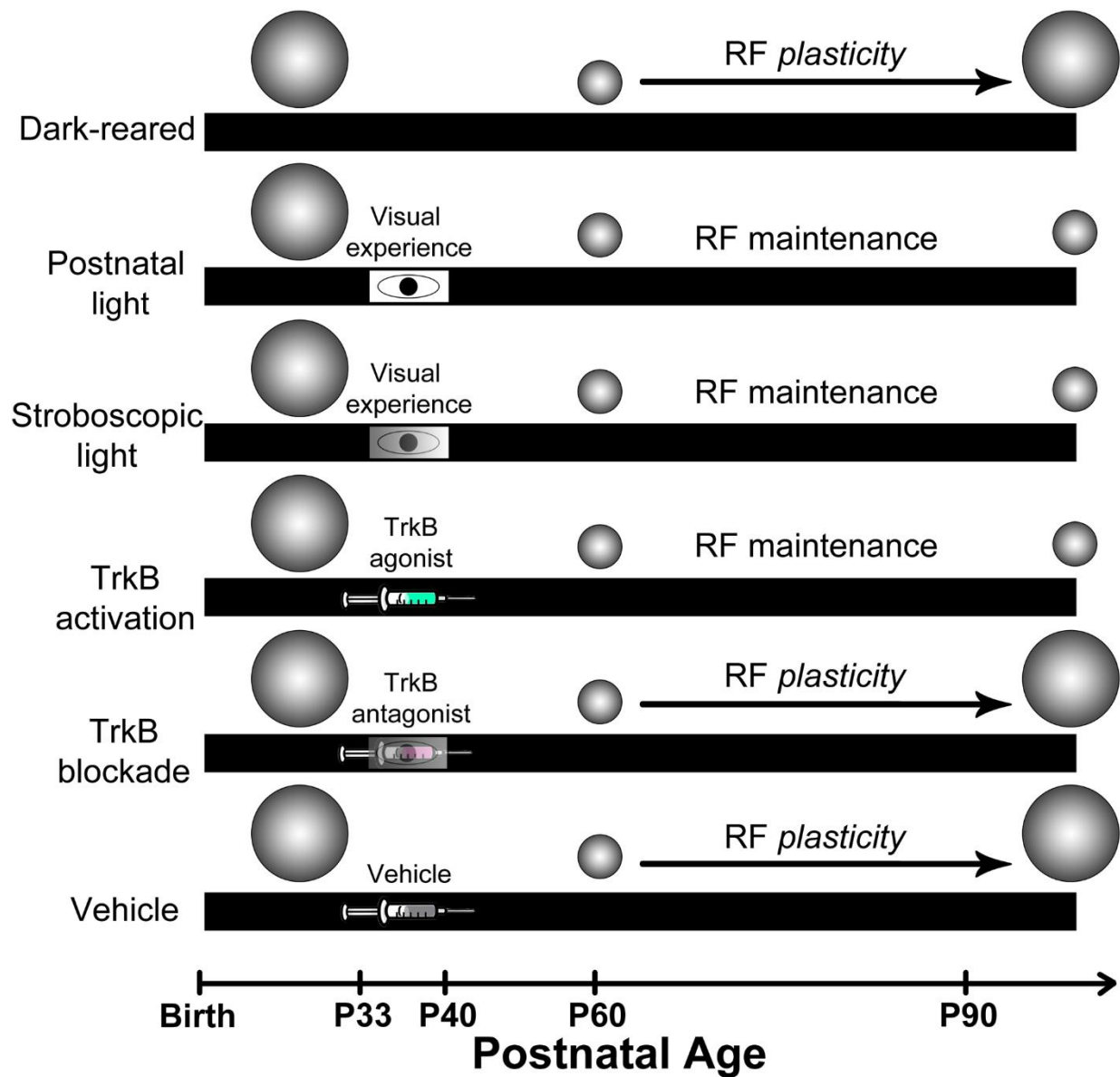


Figure 2.9: Summary. Diagram showing findings regarding the dependence of RF size maintenance in adult SC on early visual experience, and the role that TrkB activation plays within that process.

2.6 Discussion

Previously we reported that spontaneous activity alone is sufficient for RF refinement in SC and V1 (Carrasco and Pallas, 2006; Balmer and Pallas, 2015a). However, light exposure for

several days during an early critical period is necessary for maintaining refinement into adulthood (Carrasco et al., 2005). These results were surprising for two reasons; first because vision is thought to be necessary for development but not for adult maintenance of function, and secondly because early deprivation did not have any detectable effect until adulthood. These previous results provided the rationale for the current study of the mechanism through which early visual experience maintains RF size past puberty and into adulthood.

Visual deprivation can permanently impair the development of some stimulus tuning properties, yet have little effect on others, depending on species. For example, orientation selectivity in visual cortex will begin to appear in juvenile DR ferrets (Chapman and Stryker, 1993; Chapman et al., 1996; Chalupa and Snider, 1998; Issa et al., 1999; White et al., 2001) but fails to sharpen to mature levels (Huberman et al., 2008a) and direction selectivity in V1 fails to develop at all (Li et al., 2006; Van Hooser et al., 2012). Additionally, ocular dominance columns in V1 form in DR cats (Wiesel and Hubel, 1974; Horton and Hocking, 1996), but ocular dominance plasticity is prolonged into adulthood as a result (Mower et al., 1981b; Cynader, 1983). In contrast, some RF properties develop without visual experience in mice (Rocheffort et al., 2011), but continued deprivation degrades tuning in adult mice and rats (Hensch, 2005). This suggests that one role of early visual experience may be to fine tune and then stabilize previously established connections in their mature state. This maturation is often associated with increased GABAergic inhibition (Hensch et al., 1998; Fagiolini et al., 2004) initiated by increases in visually evoked BDNF and subsequent TrkB receptor activation (Huang et al., 1999). Recent work further connects early visual experience, BDNF activity, and cortical maturation persisting into adulthood (Zhang et al., 2018), though BDNF was reported to have an inverse relationship with early cortical maturation during the critical period (P23-28). We report

that increasing TrkB phosphorylation during a critical period can substitute for visual experience and forestall the negative effects of visual deprivation on RF refinement. These findings clarify the requisite role of experience-driven TrkB activity in stabilizing adult RFs and preventing deleterious adult plasticity. They suggest that TrkB receptor signaling is the convergence point through which visual activity drives the maturation of inhibition in the superior colliculus and visual cortex, at least in hamsters and mice (Gianfranceschi et al., 2003; Balmer and Pallas, 2015a).

2.6.1 TrkB signaling mediates activity-dependent maturation of visual processing circuits in V1 and SC

Development of ocular dominance columns is subject to a critical period during which monocular deprivation can shift the representation of cortical cells away from the closed eye (Wiesel and Hubel, 1963c, 1965). Dark rearing causes a prolongation of the critical period for ocular dominance plasticity, perhaps as a result of prolonged immaturity of NMDA receptors (Carmignoto and Vicini, 1992a) and GABAergic neurons (Jiang et al., 2005). In contrast, RF refinement in SC and V1 of hamsters and rats is unaffected by visual deprivation, and early experience is necessary only for stabilizing RFs in adulthood. Visual experience is thought to influence ocular dominance development through a BDNF-mediated signaling pathway that promotes maturation of inhibitory synapses and regulation of critical period plasticity. Visual input drives NMDA receptor activity, increasing BDNF levels and thus triggering maturation of inhibition (Castren et al., 1992; Greenberg et al., 2009; Park and Poo, 2013b). Transcription factors such as Npas4 regulate genes associated with plasticity, including BDNF (Lin et al., 2008; Van Hooser et al., 2012; Bloodgood et al., 2013). BDNF in turn binds to and activates TrkB receptors (Pollock et al., 2001; Viegi et al., 2002), promoting the expression of GAD,

GABA, and GABA_A receptors throughout the brain (Rutherford et al., 1997; Huang et al., 1999; Jovanovic et al., 2004; Porcher et al., 2011; Sanchez-Huertas and Rico, 2011). Critical period closure and the ensuing restriction of visual cortical plasticity are associated with visual experience-induced changes in NMDA and GABA receptor composition (Carmignoto and Vicini, 1992a; Fox et al., 1992; Stocca and Vicini, 1998; Chen et al., 2001; Li et al., 2017a), increases in GABA expression (Jiang et al., 2005), and perineuronal net development (Sur et al., 1988; Bavelier et al., 2010b; Beurdeley et al., 2012; Ye and Miao, 2013; Wen et al., 2018). Spontaneous activity is not sufficient to drive these changes in the context of ocular dominance plasticity (Sur et al., 1988; Huberman et al., 2008a; Chalupa, 2009).

The similar effects of TrkB signaling on RF refinement in both SC and V1 are surprising for a number of reasons. V1 requires several more days (P33-P40) of visual experience (12:12 hours light cycle) to stabilize adult RF refinement (>P90) than SC (P37-P40) (Balmer and Pallas, 2015a). V1 also has different GABAergic cell classes than SC, and very few of the parvalbumin positive interneurons (Mize, 1992; Choi et al., 2009; Villalobos et al., 2018) that are essential in V1 ocular dominance plasticity (Hensch, 2005b). Thus, it seems likely that there are some undiscovered differences in the TrkB signaling pathway downstream of TrkB activation.

2.6.2 How does early TrkB signaling maintain RF refinement?

Visual experience-regulated TrkB activity may function in either a permissive or an instructive role at different stages of visual system development. In the permissive role scenario, (Huang et al., 1999; Seki et al., 2003) experience driven activity increases overall BDNF production and subsequent TrkB activity. The TrkB activity would then permit maturation of the GABAergic synapses necessary to develop or stabilize RF properties. In the instructive role scenario (Kossel et al., 2001), visual experience would drive TrkB activity to form specific

ensembles of visual neurons that respond to different types of visual input. Our finding that early TrkB activity maintains RF refinement in adult SC suggests that the BDNF-TrkB signaling pathway plays more of a permissive than an instructive role. This view is supported by our previous result that RF refinement will occur without any visual experience in SC (Carrasco et al., 2005) and in V1 (Balmer and Pallas, 2015a) and that the loss of refinement in DR adults coincides with reductions in GABA expression and postsynaptic GABA receptor function. Thus RF refinement does not require instructive signaling from the BDNF-TrkB signaling pathway to occur, but rather requires permissive signaling to maintain its stability long term.

2.6.3 How does early visual experience contribute to survival?

In early life, most mammals have underdeveloped sensory and motor capabilities, and require intensive parental care to survive. As they age, sensory and motor abilities mature in response to intrinsic maturational processes as well as in response to environmental stimuli, leading to improved overall function and independent survival in adulthood. Vision is one of the most important senses for many mammals, because it facilitates object and feature detection for purposes of conspecific and interspecific interactions, as well as for feeding and locomotion (Thinus-Blanc, 1996). Improvements in visual acuity, as well as orientation, size, and motion tuning, are all important for identifying objects in the environment, and require varying amounts of early visual experience to develop (see Huberman et al., 2008a, for review). In SC, the multisensory integration of vision with other senses considerably enhances the salience of a sensory event (Meredith and Stein, 1983; Frens and Van Opstal, 1998) and is important for orientation behaviors (Stein et al., 1989). Among these behaviors, looming stimulus detection and fear responses allow the avoidance of aerial predators (Yilmaz and Meister, 2013).

Although the function of looming detection is well understood, the contribution of TrkB activity to development of this behavior during early development has yet to be explored. Our results show how early visual experience, increased TrkB signaling, and refined RFs in SC are essential for the performance of looming stimulus detection and the defensive behaviors associated with it. Surprisingly, our results indicate that looming response behaviors in mice, a nocturnal species with presumably less reliance on vision, were more detrimentally affected by dark rearing compared to hamsters. This could be due to poorer overall visual acuity, or perhaps reduced dorsal visual field coverage in mice, something we will explore in future work. Interestingly, of the two different fear response behaviors assessed here, the freezing response was reduced, and the escape response was nearly eliminated in DR animals. Freezing is uniquely effective as a defense from aerial predators (Eilam, 2005; De Franceschi et al., 2016), and our finding that it becomes the dominant response for DR animals raises the possibility that it could be a more instinctual behavior than escape responses. Another possibility is that dark rearing alters the downstream processing pathway that facilitates the behavioral response. For example, the SC-ventral midline thalamus connection processes the overall reaction to visual threats (Salay et al., 2018), and could be affected by downstream TrkB activity. Future experiments will address these unanswered questions and further our understanding of TrkB signaling during early development.

**3 EARLY VISUAL EXPERIENCE MAINTAINS ADULT RECEPTIVE FIELD
REFINEMENT IN V1 AND SC BY MAINTAINING GABA EXPRESSION RATHER
THAN BY ALTERATIONS IN GABA_A RECEPTORS, CHLORIDE PUMPS, OR
NMDA RECEPTORS**

David B. Mudd, Parag Juvale, Nitheyaa Shree, and Sarah L. Pallas

Author contributions: David B. Mudd, Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – editing & review. Parag Juvale, Investigation, Formal analysis, Writing – editing & review. Nitheyaa Shree, Investigation. Sarah L. Pallas, Conceptualization, Funding acquisition, Writing – original draft, Writing – editing & review.

3.1 Abstract

RFs in superior colliculus (SC) and visual cortex (V1) refine normally in DR hamsters, but RF size can only be preserved in adulthood with brief light exposure during a CP. RF enlargement in SC is caused at least in part by a loss of lateral inhibition, but previous results suggested a loss of efficacy in GABAA receptors as an additional component of this detrimental form of adult plasticity. To address this hypothesis we examined GABAA receptor levels, location, and subunit composition using Western blotting. In addition, we assayed the GABAA receptor anchoring protein gephyrin. To test the alternate hypothesis that adult RFs enlarge as a result of immature NMDA receptors, we examined NR2A/2B ratios and levels of the anchoring protein PSD-95. We further examined the expression of chloride pumps KCC2 and NKCC1 to identify whether differences in the chloride gradient may account for GABAA receptor efficacy losses. We found that DR induced RF enlargement does not result in alterations in GABAA receptor endocytosis or subunit composition, nor does it change the expression of gephyrin, PSD-95, or the chloride pumps KCC2 and NKCC1. Our results suggest that postsynaptic modifications may not be as important for regulating RF refinement as total GABA expression is in SC.

3.2 Introduction

During brain development, synaptic strength and selectivity mature together and are influenced by early spontaneous and sensory-evoked neural activity (review Wong and Ghosh, 2002; Ruthazer and Cline, 2004; review Blankenship and Feller, 2010). Sensory experience is vital during early “critical periods” for neural circuits to develop normally. The visual pathway is one of the most extensively studied systems for understanding critical period regulation (see Hensch, 2005b for review). In this study, we address the influence of early visual experience

and the effects of visual deprivation on the long-term stability of excitatory and inhibitory postsynaptic elements in superior colliculus (SC) of an altricial rodent species (Syrian hamsters).

Receptive field (RF) refinement involves the progressive contraction in RF size from early in development, and is critical for sharpening visual acuity (Daw, 2006). Although visual experience was thought to be necessary for this process (Teller et al., 1978; Timney et al., 1978; Fagiolini et al., 1994), we found that in chronically dark reared (DR) Syrian hamsters, RF refinement occurs normally in both SC (Carrasco et al., 2005) and V1 (Balmer and Pallas, 2015a). However, visual experience is required to maintain RF refinement in adulthood (>P60), unless light exposure is provided during an early critical period (P33-P40) (Carrasco and Pallas, 2006). Without early visual experience, RFs expand and visual acuity is decreased (Mudd et al., 2019). RF re-expansion results at least in part from a loss of GABAergic inhibition within (Carrasco et al., 2011; Balmer and Pallas, 2015b). However our previous study of changes in inhibitory signaling following RF re-expansion also described decreases in GABA receptor efficacy in visually deprived adults. Here we explore whether the stability of GABA_A receptor function in adulthood requires light exposure during a critical period.

Synaptic inhibition throughout the visual pathway is primarily mediated via the neurotransmitter γ -aminobutyric acid (GABA). GABA signaling is mediated by fast acting chloride (Cl⁻) channels (GABA_A receptors) (Pfeiffer et al., 1982; Sigel et al., 1982), or by slow moving metabotropic G-protein coupled receptors (GABA_B receptors) (Couve et al., 2000; Bettler and Tiao, 2006). GABA_A receptors are part of the cys loop ligand-gated ion-channel family and are comprised of a pentameric structure in which five subunits are arranged around a central pore. The subunit composition of GABA_A receptors can affect their functional properties (Farrant and Nusser, 2005), location, and membrane trafficking (Jacob et al., 2005). In the

present study we tested whether early visual experience is required for normal GABA_A receptor composition, trafficking across the membrane, and anchoring at the postsynaptic membrane using Western blots to assay levels of receptor subunits and other postsynaptic components of inhibitory and excitatory synapses in SC and V1.

We find that the subunit composition, synaptic and extrasynaptic localization, and endocytosis of GABA_A receptors remain functionally unchanged in adult dark reared hamsters with re-expanded RFs. We further find that levels of the synaptic scaffolding proteins gephyrin and PSD-95 remain unchanged, as does the adult expression levels of Cl⁻ pumps (KCC2/NKCC) and NMDA receptor subunits (NR2A/NR2B). These findings suggest that the loss of RF refinement in adulthood may be primarily mediated by reductions in overall GABA expression.

3.3 Materials and Methods

3.3.1 Subjects

A total of (42) adult Syrian hamsters (*Mesocricetus auratus*) of both sexes were bred within our animal facility and used as subjects in this study. Hamsters As a model for studying the developing visual system, Hamsters are valuable due to their robust and well-characterized visual responses and short gestation time (Pratt and Lisk, 1989). Hamsters were housed in social groups of up to 5 adults per cage in standard rodent cages with a variety of enrichment items that were changed regularly, along with bedding and cage. All animals were provided with ad libitum access to food and water.

3.3.2 Treatment groups

All animals were bred in-house to control sensory experiences from P0. Dams of dark reared subjects were transferred into a completely dark room 1-3 days before parturition. The

dark room was comprised of a standard facility housing room with all sources of normal light removed. An antechamber and light-impenetrable black curtain separated the housing room from the hallway, ensuring any accidental openings of the hallway doors did not affect the housing room. Within the dark room, animals were housed inside light-tight stackable cages with a standard HVAC filtration system consistent with the other animal rooms in the animal facility. During general animal husbandry purposes the hamsters were exposed to dim red light at a wavelength not visible to Syrian hamsters (Huhman and Albers, 1994). Light-exposed (LE) hamsters were transferred into a standard 12/12 light cycle room for the duration of the critical period for RF refinement maintenance in SC and V1 (P33-P40) (Carrasco et al., 2005; Balmer and Pallas, 2015a). Subjects were then transferred back into the dark room and housed there until >P90.

3.3.3 Western blotting

Animals were euthanized with a sodium pentobarbital-and phenytoin sodium-containing mixture (Euthasol >150 mg/kg IP). Brains were immediately extracted and frozen in 2-methylbutane on dry ice, then stored at -80°C or immediately dissected for preparation of lysates. Individual left and right superficial SC were excised and lysed in RIPA buffer (150mM NaCl, 150mM Tris, 1% NP-40, 0.1% SDS, 0.5% sodium deoxycholate) containing 2% Halt protease inhibitor (ThermoFisher Scientific). Lysates were centrifuged at 16,000g for 15 minutes at 4°C, with the resulting supernatant saved as the cytosolic fraction of the lysed cells. The pellet was resuspended in 2mM HEPES buffer and ultracentrifuged at 70,000 rpm for 45min at 4°C with the supernatant discarded and the pellet resuspended in 0.5mM HEPES buffer and saved as the membrane fraction. Protein bands were labeled using IRdye fluorescent secondaries (Li-Cor) and imaged on an Odyssey CLx fluorescent imaging system (Li-Cor). Protein expression levels

were quantified as the optical density of the labeled protein normalized against the optical density of the housekeeping protein such as GAPDH or β -actin using ImageJ.

Primary antibodies used in this study included: Rabbit anti-GABA_AR α 1 (1:1000, Cat#: AGA-001, Alomone Labs); Mouse anti-KCC2 supernatant (1:50, Cat#: 75-013, NeuroMab/UC Davis); Mouse anti-NMDAR2B (1:1000, Cat#: ab93610, Abcam); Rabbit anti-NKCC1 (1:1000, Cat#: ab59791, Abcam); Mouse anti-PSD-95 (1:500, Cat#: ab2723, Abcam); Rabbit anti-NMDAR2A (1:1000, Cat#: ab133265, Abcam).

3.3.4 Statistical Analysis

A Student's *t*-test was used to compare parametric data with equal variance between treatment groups and a normally distributed data set. Descriptive statistics for these analyses are provided as mean \pm standard error of the mean (SEM).

3.4 Results

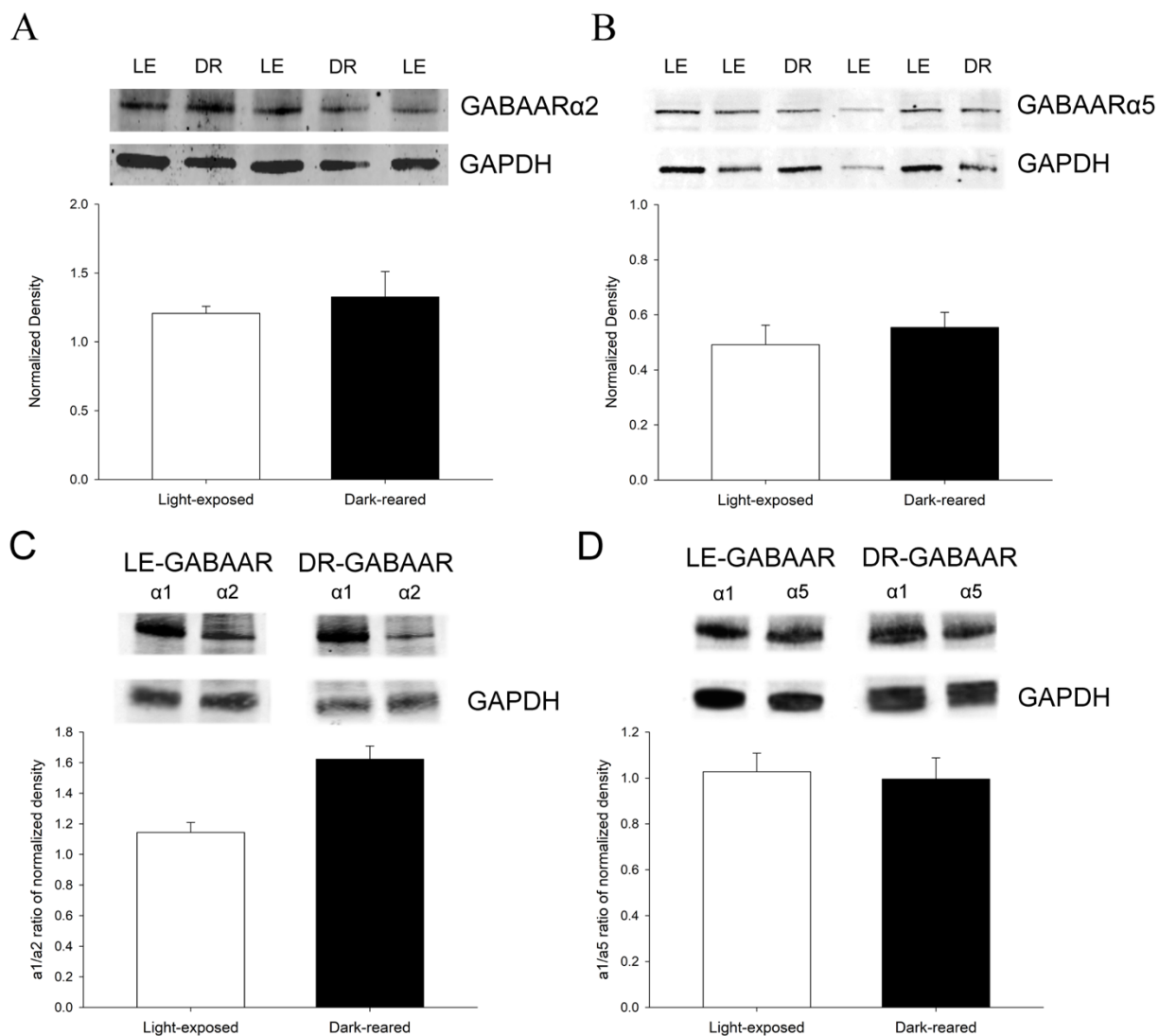
Normal brain function relies on the precise regulation of excitatory and inhibitory neuronal activity. Although neurological signaling is initiated by excitatory neurotransmission (glutamate), inhibitory neurotransmission (GABA) is arguably more important for shaping activity-dependent events in development – primarily because it prevents circuits from becoming overexcited (Hensch et al., 1998; Bannai et al., 2009; Huang, 2009). The circuits underlying RFs in SC and V1 require experience to maintain their maturational refinement in adulthood (Carrasco et al., 2005; Balmer and Pallas, 2015a), and this maintenance has been shown to involve changes in overall GABA expression and GABA_A receptor function (Carrasco et al., 2011), but the exact nature of these changes is unknown. The results presented in this study examine several possible ways that visual deprivation during a critical period for RF refinement could affect inhibitory signaling in adult SC.

3.4.1 *Dark rearing does not affect the subunit composition of GABA_A receptors in adult SC*

GABA_A receptors function as the primary mediator of phasic inhibition in the adult brain. They are built as a pentameric receptor of five subunits grouped around a central chloride ion pore, and the functional characteristics of the receptor largely depend upon the composition (Sigel et al., 1990) and organization (Minier and Sigel, 2004) of the subunits. Of the many subunit arrangements, alpha1 and 2 subunits have been primarily associated with synaptically localized receptors, however they function differently and are expressed at different points in development. In rats, receptors containing the alpha2 subunit are widely expressed at birth, whereas alpha1 has low expression and is restricted to a few brain areas (Fritschy et al., 1994). During the first several postnatal weeks, alpha1 expression sharply increases, coinciding with a reduction in alpha2 expression. This alpha2-alpha1 switch in dominant subunit expression underlies a developmental decrease in inhibitory post synaptic current (IPSC) decay time and an increase in IPSC amplitude in thalamus (Okada et al., 2000). We reasoned that could the alpha2-alpha1 switch, if recapitulated in adulthood, underlie the reduction in GABA_A receptor function that we have previously observed in our studies of RF refinement loss in SC and explored the possibility by examining the expression of each in DR adults. Hamsters in the visual deprivation group were dark reared (n=5) from birth and hamsters in the LE control group (n=6) were moved to normal 12:12 housing during the critical period for adult RF refinement maintenance (P-33-P40). We then allowed the subjects to continue developing in a DR environment until adulthood (>P90), then used Western blotting to measure the amount of membrane-bound alpha1 and alpha2 GABA_A receptor expression in adult SC. We found that there were no significant differences in either the overall expression of alpha2 (LE: 1.25 ± 0.089 , n=8) (DR: 1.155 ± 0.249 , n=8) (T=74, n(small)=8 n(big)=8 p=0.574 Mann-Whitney Rank Sum

Test) (**Figure 3.1A**), or the ratio of alpha1/alpha2 expression in the SC between adult DR (1.624 ± 0.171 , n=2) and LE (1.144 ± 0.131 , n=2) ($T=3.0$, n(small)=2, n(big)=2, $p=0.333$) hamsters (**Figure 3.1C**). These findings suggest that there is no change in the normal developmental transition from alpha2 to alpha1 dominant expression in the experience dependent maintenance of RF refinement maintenance in adult SC.

GABA_A receptors can also be expressed extrasynaptically, where they can be activated by ambient GABA derived from synaptic spillover or other non-neuronal sources. This low concentration GABA activity generates “tonic” inhibition (Farrant and Nusser, 2005), and constitutes a significant (75%) percentage of the total inhibitory forces acting on neurons in hippocampus (Mody and Pearce, 2004; Magnin et al., 2019). Alpha5 subunit containing receptors are primarily expressed extrasynaptically and have been implicated in regulating the induction of synaptic plasticity for memory in hippocampus (Saab et al., 2010; Zurek et al., 2012; 2014). To investigate the possible role of alpha5 levels in adult RF maintenance we performed Western blotting and compared between DR (0.492 ± 0.071 , n=12) and LE hamsters (0.554 ± 0.0549 , n=11) ($t(21)= 0.687$, $p=0.5$, t-test) (**Figure 3.1B**). We found no significant differences between groups in alpha5 protein levels. We also compared the ratio of alpha5/alpha1 between LE (1.027 ± 0.082 , n=10) and DR (0.995 ± 0.0926 , n =9) hamsters and found no differences between these groups ($t(17)=0.259$, $p=0.799$, t-test) (**Figure 3.1D**). These results taken together suggest that the alpha1/2/5 subunit expression of GABA_A receptors in SC is not being modulated by early visual experience, and does not impact adult receptor function.

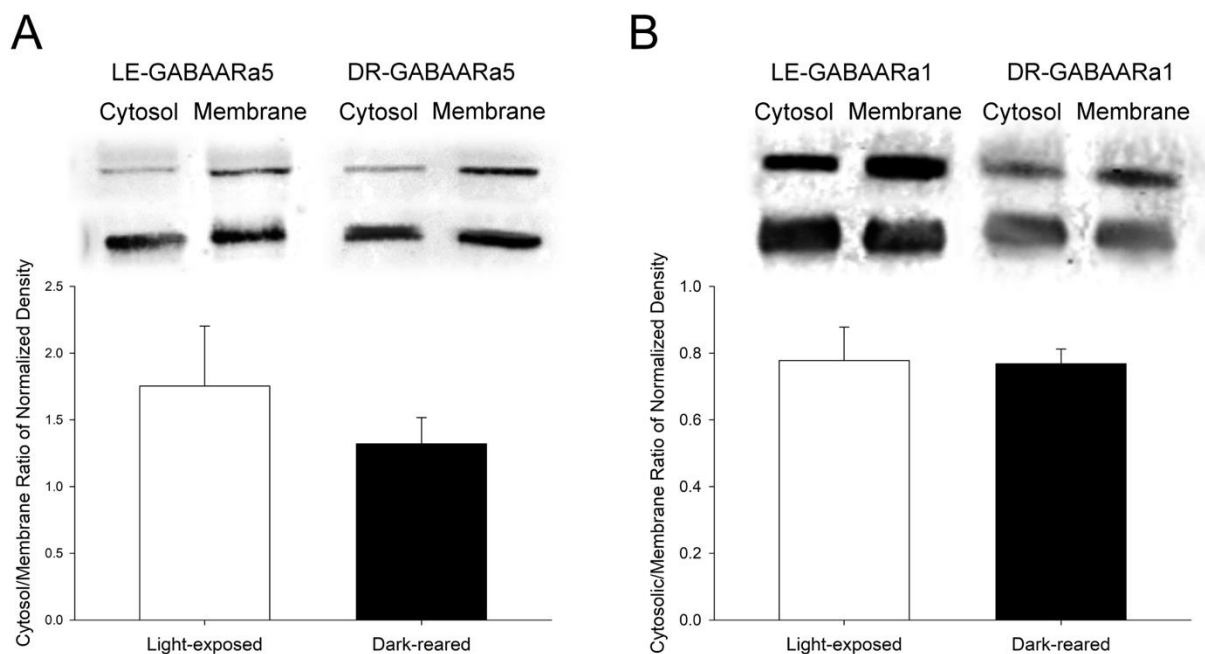


3.1: Adult GABA_A receptor subunit composition is not affected by early dark rearing. Example blots of LE and DR treatment groups generated using 20 μ g of SC protein per lane and densitometric analyses of the differences in labeled proteins. GABAAR subunits measured and compared include: (A) GABAAR α 5 protein comparison, (B) GABAAR α 2 comparison, (C) GABAAR α 5 : GABAAR α 1 ratio, (D) GABAAR α 2 : GABAAR α 1 ratio. All presented lanes are from the same gel(s), and each measured protein was normalized against GAPDH as a loading control. Data presented as mean \pm SEM.

3.4.2 The endocytosis-mediated rate of trafficking synaptic and extrasynaptic GABA_A receptors is similar in normal and dark reared adult SC

The regulation of GABA_A receptors at the synapse is pivotal for maintaining correct levels of inhibitory synaptic transmission and overall physiological function (Jacob et al., 2008). Impaired trafficking of GABA_A receptors could affect their synaptic localization in SC and thus their overall response to synaptically released GABA. GABA_A receptor trafficking is partially regulated by endocytosis: the controlled removal of receptors from the membrane. Receptors are subsequently reinserted into the membrane or undergo lysosomal degradation after longer periods (Kittler et al., 2004). We reasoned that if endocytosis were dysregulated, either by decreased receptor reinsertion, or increased receptor degradation, it could negatively impact the efficacy of GABA_A receptors at the synapse. We examined this possibility by comparing the ratio of membrane-bound to cytosolic alpha1 subunit containing receptors between our treatment groups. We observed no differences in the membrane/cytosolic ratio of alpha1 expressing receptors between DR (0.768 ± 0.044 , n=7) and LE (0.778 ± 0.1 , n=6) adult hamsters ($t(11)=0.948$, $p=0.926$, t-test) (**Figure 3.2A**).

We also examined the possibility that extrasynaptic alpha5 receptor endocytosis-mediated trafficking may be dysregulated and responsible for changes in tonic GABA_A inhibition. Again we found no differences in DR (1.320 ± 0.198 , n=8) and LE (1.753 ± 0.449 , n=6) groups ($t(12)=0.968$, $p=0.352$, t-test) (**Figure 3.2B**). These results indicate that the overall endocytosis-mediated trafficking of alpha1 (synaptic) and alpha5 (extrasynaptic) subunit expressing GABA receptors is not responsible for the decreased efficacy of GABA_A receptors observed in RFs that fail to maintain refinement following dark rearing.



3.2: Endocytosis of synaptic and extrasynaptic GABA_A receptors is not affected by early dark rearing.

(A) Adult levels of the intracellular/membrane attached ratio of GABAARα5 and **(B)**

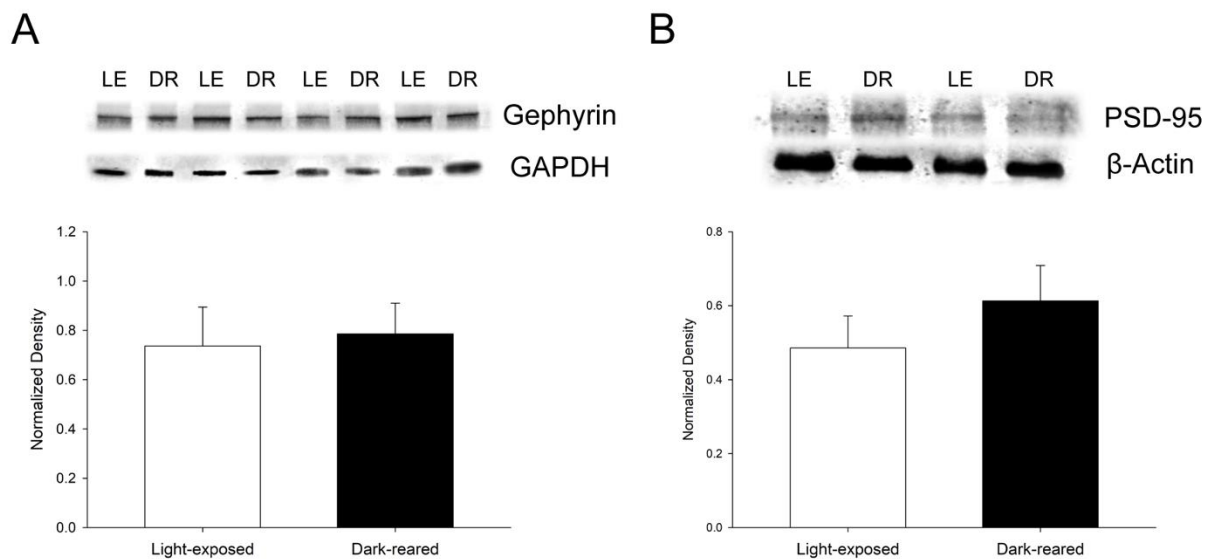
GABAARα1 expression was not affected by early light deprivation. Example blots represent bands of labeled intracellular and membrane bound proteins from the same animal, measured as a ratio and compared between LE and DR groups. Loading control measured against GAPDH (lower band). Data presented as mean relative optical density \pm SEM.

3.4.3 Inhibitory and excitatory scaffolding proteins in SC are not affected by dark rearing

One factor influencing the accumulation and confinement of GABA_A receptors at postsynaptic sites is the membrane scaffolding protein gephyrin (Kneussel et al., 1999; Sun et al., 2004; Jacob et al., 2005; Tretter et al., 2008). Decreased expression of gephyrin results in less clustering (Essrich et al., 1998) and more overall mobility of GABA_A receptors at the synapse (Jacob et al., 2005). We surmised that decreased gephyrin expression could be responsible for the weaker GABA_A receptor signaling we have observed in neurons with RFs that fail to

maintain refinement. Using Western blotting we compared membrane-bound gephyrin expression between DR and LE adults. DR adults (0.786 ± 0.124 , $n=17$) were similar to LE adults (0.736 ± 0.158 , $n=16$) ($t(31)=-0.247$, $p=0.806$, t-test) (**Figure 3.3A**), a surprising result considering our understanding that dark rearing reduces overall GABAergic inhibition. This result indicates that adult gephyrin expression is not affected by dark rearing during the critical period for RF refinement maintenance, and that if GABA_A receptor accumulation and trafficking is being affected, then it is in a gephyrin-independent manner.

PSD-95 is the primary excitatory (AMPA and NMDA) receptor scaffolding protein in neurons (Chen et al., 2015), and functions in a similar way as gephyrin does for GABA receptors. Although it does not have a direct impact on GABA_A receptor function, PSD-95 has been shown to have an influence on visual plasticity. For example, mice lacking PSD-95 have lifelong ocular dominance plasticity in V1 that results from an increase in the overall expression of silent (AMPA-free) synapses, but completely normal inhibitory tone (Huang et al., 2015b). We examined the possibility that the plasticity involved with the dark rearing-induced re-enlargement of RFs could also be mediated by a reduction in adult PSD-95 expression. We found that PSD-95 was not significantly different in DR (0.613 ± 0.96) compared to LE adult hamsters (0.486 ± 0.868) ($t(17)=-0.978$, $p=0.342$, t-test) (**Figure 3.3B**). These results suggest that a PSD-95 mediated return to silent synapses does not underlie the re-enlargement of RFs in SC following early dark rearing.



3.3: Adult gephyrin and PSD-95 expression is not affected by early dark rearing.

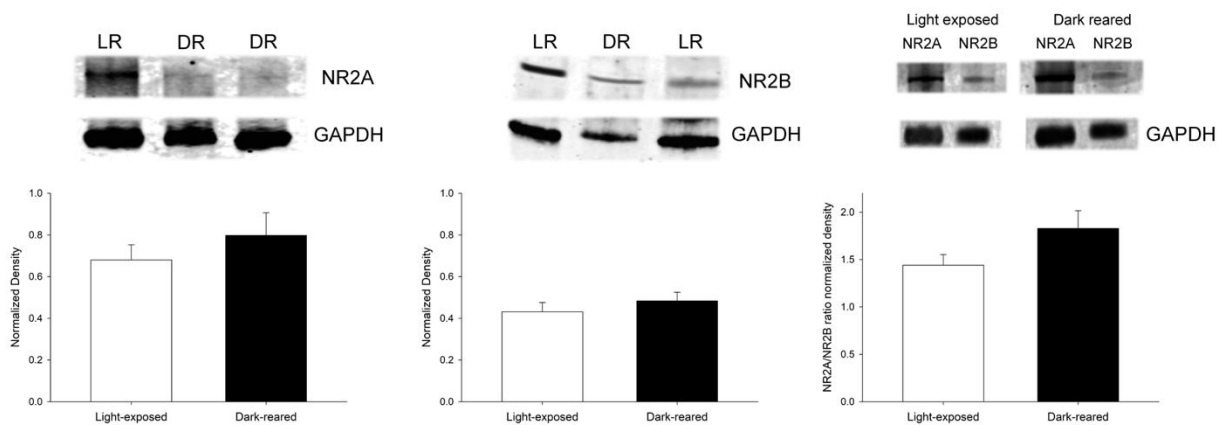
(A) Gephyrin and (B) PSD-95 expression was consistent between adult (>P90) LE and DR

groups. GAPDH and β -actin were used as loading controls. Data presented as mean relative optical density \pm SEM.

3.4.4 NMDA receptors in adult SC have normally matured subunit compositions following dark rearing

Excitatory plasticity could also contribute to enlargement of RFs during DR (Huang and Pallas, 2001b). In V1, dark rearing disrupts the substitution of the NMDA receptor NR2A subunit for the NR2B subunit that normally occurs postnatally, limiting NMDAR-dependent excitatory plasticity (due to the shorter open time of NR2A) (Carmignoto and Vicini, 1992b; Philpot et al., 2001). Thus, lower NR2A expression relative to NR2B could cause RFs to expand through potentiation of excitatory synapses. Our results indicate that the total expression of NR2A in LE (0.680 ± 0.073 , $n=8$) and DR (0.798 ± 0.109 , $n=6$) adult hamsters are similar, as are the expression levels of NR2B (LE: (0.431 ± 0.0445 , $n=8$) DR: ($0.484 \pm (0.0406)$) ($t(12)=-0.842$,

$p=0.416$, t-test) (**Figure 3.4A,B**). The ratio of NR2A/NR2B expression between DR (1.829 ± 0.186 , $n=5$) and LE hamsters (1.440 ± 0.112 , $n=6$) was also similar in adult SC ($t(9)=-1.862$, $p=0.095$, t-test) (**Figure 3.4C**).



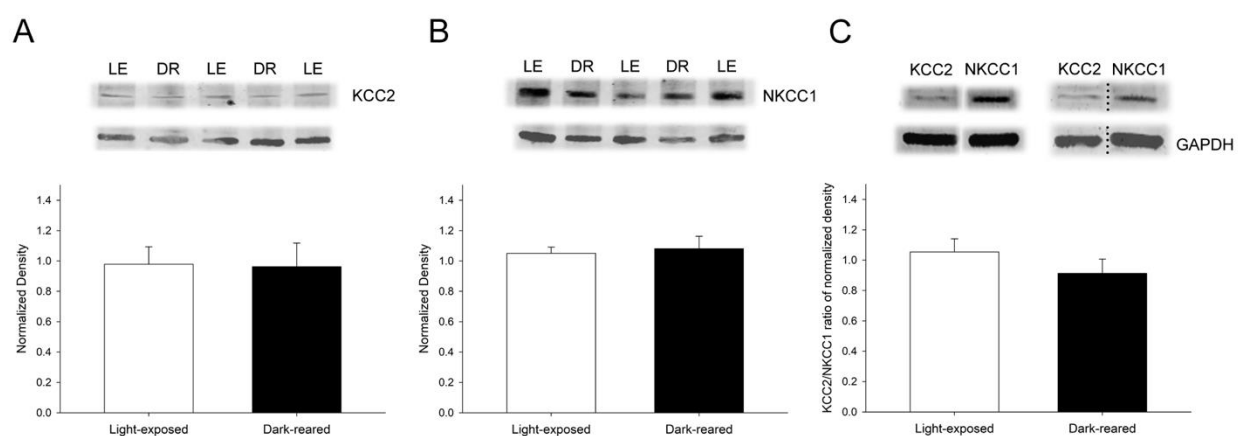
3.4: Adult NMDAR subunit compositions are not altered by early dark rearing.

Western blot examples and densitometric analyses of (A) NR2A, (B) NR2B, and (C) the ratio of NR2A/NR2B expression in adult (>P90) LE and DR hamsters. Data presented as mean relative optical density \pm SEM.

3.4.5 Chloride pumps maintain normal development ratios in adult dark reared subjects

Inhibitory GABAergic signaling in neurons is dependent upon the intracellular chloride (Cl^-) concentration. The $\text{K}^+ \text{Cl}^-$ co transporter (KCC2) is responsible for regulating intracellular Cl^- in mature adult neurons by using an outward K^+ current (Rivera et al., 1999), and also regulates the formation, function, and plasticity of glutamatergic synapses (Li et al., 2007; Gauvain et al., 2011; Chevy et al., 2015). Early in development GABA_A receptors are excitatory because the $\text{Na}^+ \text{K}^+ 2\text{Cl}^-$ co transporter 1 (NKCC1) (which mediates Cl^- uptake) is dominant, and during the first several weeks after birth is replaced by KCC2 as the dominant Cl^- pump in the brain, shifting GABA_A receptors to become inhibitory (Rivera et al., 1999). Recent findings

reveal that in V1, the developmental switch from dominant NKCC1 to dominant KCC2 occurs at the same time as a period of BDNF/TrkB mediated synaptic imbalance – a crucial critical period for the transition of immature neurons to a more mature state (Zhang et al., 2018). We surmised that a shift in the ratio of KCC2:NKCC1 could underlie the reopening of plasticity for RF size refinement in adulthood, leading to re-enlargement of RFs in SC. We examined the expression of KCC2 and NKCC1 in adult SC neurons and observed no significant differences between our treatment groups. LE and DR hamsters had no differences in either KCC2 ($t(14)=0.082$, $p=0.936$, t-test) (**Figure 3.5A**) or NKCC1 ($t(14)=-0.339$, $p=0.740$, t-test) (**Figure 3.5B**), or in the ratio of the two chloride pumps within groups ($t(8)=1.096$, $p=0.305$, t-test) (**Figure 3.5C**).



3.5: Adult chloride pump expression is not affected by early dark rearing.

Western blot examples of LE and DR samples labeled against chloride pumps (A) KCC2 and (B) NKCC1, (C) and a comparison of the within subject ratio of KCC2:NKCC1 in LE and DR adult (>P90) hamsters. Data presented as mean relative optical density \pm SEM.

3.5 Discussion

Critical period plasticity is generally regarded as a balancing act between excitation and inhibition, where both excitatory and inhibitory circuits are shaped by sensory experiences after

the critical period opens. As the critical period closes, inhibitory circuitry matures and places brakes on the established synaptic connections to stabilize them throughout life. In visual development, the GABAergic inhibitory system modulates the development of several RF detection properties, such as direction selectivity, orientation selectivity, and ocular dominance plasticity in the visual cortex (V1) (Wolf et al., 1986; Iwai et al., 2003; Hensch and Stryker, 2004). Previous experiments have established a correlation between RF refinement maintenance and GABA expression in SC (Carrasco et al., 2011; Mudd et al., 2019) and V1 (Balmer and Pallas, 2015a), however the specific changes in circuitry had not been extensively examined. We report that RF refinement maintenance in SC does not appear to involve changes in GABA_AR subunit composition, inhibitory or excitatory scaffolding protein expression, chloride pump ratios, or the subunit composition of coincidence detecting NMDARs. These findings exclude several possible mechanisms that could explain the reduced GABA_AR signaling reported in DR adult SC (Carrasco et al., 2011), and emphasizes that sustained GABA expression is the primary mechanism underlying TrkB mediated RF refinement maintenance (Mudd et al., 2019).

3.5.1 GABA expression in maintaining RF refinement in adulthood

GABA-GABA_AR interaction is known to regulate various downstream signaling pathways and a major regulator of GABA signaling is BDNF-TrkB signaling. These data suggest a positive excitatory feedback loop between GABA and BDNF expression during early development, where GABA facilitates BDNF expression, and BDNF facilitates the synaptic release of GABA. Signaling via the MAPK cascade and the transcription factor CREB appear to play a substantial role in this process (Obrietan et al., 2002). In early development, GABA and TrkB pathways are active in conjunction with each other and affect multiple cellular actions including proliferation, migration, and synaptic plasticity (Porcher et al., 2011).

BDNF-TrkB interaction leads to dimerization and auto-phosphorylation of the receptor, thereby triggering MAPK, PLCgamma and PI3K pathways (Yoshii and Constantine-Paton, 2007). These pathways in turn lead to the activation of a multitude of downstream effectors and mediators to finally initiate a CREB-dependent transcription process that leads to the increase in GABA_AR subunits as well as more BDNF production. In addition to this, an increase in the GABA_AR surface levels is mediated BDNF-dependent inhibition of receptor endocytosis and the continued and unaffected reinsertion of the receptor into the membrane (Porcher et al., 2011). This positive feedback regulation is critical in developing neurons and hence constituted a major part of this work. The GABA_AR subunit composition in neither the synapse nor the extrasynaptic regions was affected due to dark rearing; nor did the NMDA receptors or Chloride channels change in number. This leads to one possibility that probably GABA expression levels alone are a key factor in RF re-enlargement, as our previous works have indicated (**Carrasco et al., 2011; Mudd et al., 2019**).

Since BDNF signaling is known to elicit proliferation and synaptic plasticity-associated responses via multiple pathways resulting in the activation of cAMP-responsive element-binding protein (CREB), actin-binding proteins, and mammalian (mechanistic) target of rapamycin (mTOR), synaptic plasticity-associated downstream cellular targets like molecules involved in actin polymerization like Tiam1, Rac1, eIF4E and 4EBP1 should also be investigated. A key finding of this work is that the presynaptic and the postsynaptic scaffold proteins PSD-95 and gephyrin did not have altered expression levels in adulthood following early sensory deprivation, suggesting that changes in inhibitory function are likely not caused by a gross change in glutamatergic or GABAergic synaptic density. Alternatively, the clustering of GABA_ARs at inhibitory synapses in SC may happen in a gephyrin-independent manner (Zita et al., 2007), or

total gephyrin expression may not be as important as the formation of gephyrin nanodomains within inhibitory synapses (Pennacchietti et al., 2017). Future studies with different techniques would be required to determine if changes in receptor clustering may be occurring and to what extent gephyrin or PSD-95 may have in mediating such effects.

4 DISCUSSION

Sensing the environment and executing behaviors relies on fine-tuned neuronal connectivity. Understanding the molecular and cellular mechanisms that underlie the experience-dependent establishment of neuronal connectivity is a strong first step toward understanding how the nervous system is organized. In my dissertation, I chose the visual system of the vertebrate brain as a model to study the basic principles governing neural circuitry formation, refinement, and stabilization, largely because of the relatively simple organization of these neural tissues and the availability of reliable visual behaviors. The overarching goal of my dissertation work was to identify the molecular mechanisms governing the effects of early visual experience on RF refinement maintenance, and how those early signaling mechanisms ultimately stabilized mature RFs by preventing maladaptive plasticity in adulthood.

In this dissertation, I investigated the mechanisms underlying the experience-dependent maintenance of RF refinement in SC. Similar to what has been reported in V1, the activation of the TrkB signaling pathway during an early critical period was sufficient for RFs in SC to maintain a smaller (mature) size into adulthood, even after dark rearing from birth. I also go on to examine the necessity of TrkB signaling in RF refinement maintenance. Additionally, I showed how RF size is crucial to both SC and V1-dependent visual behaviors in adults. My work also explored the possible mechanisms governing the adult maintenance of RF refinement and provides evidence supporting the overall stability of total GABA expression as a principle force in restricting adult plasticity in SC. In sum, I found that the TrkB signaling pathway is crucial for the experience-dependent maintenance of RFs in adulthood, that maintaining RF refinement ensures proper visual behavior (even absent prior visual experience), and that

maintaining adult levels of GABA expression is important for preventing TrkB-mediated adult plasticity in the visual system.

4.1 Early TrkB activity is both necessary and sufficient for maintaining visual RF refinement in SC

My dissertation work addressed a long-standing question in the field of visual neuroscience: how does early sensory experience regulate the development and stability of the visual system? Important advances in this area of research suggest a significant role for the experience-driven maturation of adult inhibition in the formation of matured visual circuits (Hensch et al., 1998; Gao et al., 1999; Morales et al., 2002; Maffei et al., 2006) and their stabilization throughout adulthood (Carrasco et al., 2011; Balmer and Pallas, 2015a). This phenomenon has been extensively studied in V1, where the maturation of inhibition appears to be regulated, at least in part, by early experience-driven BDNF/TrkB signaling (Rutherford et al., 1997; Huang et al., 1999; Yoshii and Constantine-Paton, 2010). Studies have reported that BDNF is essential for changes in inhibitory synapse strength to occur in early development (Gao et al., 2014) and that it can be protective against the negative effects of dark rearing on V1 function (Gianfranceschi et al., 2003). However, it remains unknown whether early BDNF/TrkB signaling is an important signaling mechanism throughout the entire visual pathway, or if its role stabilizing circuit maturation is limited to V1.

To study the role of TrkB signaling on visual development outside of V1, we chose to examine the maintenance of RF refinement in SC, but rather than simply utilizing a transgenic animal model to indiscriminately increase endogenous BDNF expression from birth, we chose to pharmacologically manipulate TrkB activation during exclusively throughout the critical period. We find that activating TrkB receptors during the critical period in DR hamsters is sufficient to

prevent adult plasticity in SC, resulting in mature RFs persisting into adulthood, a finding consistent with previous reports in V1 (Gianfranceschi et al., 2003). We go on to find that providing visual experience during the critical period fails to prevent adult plasticity when TrkB receptor activity is blocked, resulting in enlarged RFs in adulthood. These results support the hypothesis that TrkB activity may serve as a common signaling mechanism promoting experience-driven development throughout the visual circuit.

We also find that TrkB mediated prevention of adult plasticity results in mature (higher) levels of GABA expression in adult SC a finding consistent with the effects of early visual experience (Carrasco et al., 2011), and suggests that they both express similar levels of GABAergic inhibition in adults. In support of this, we also observe that modulating TrkB activity during the critical period also does not alter the expression of synaptic GABA_A receptors in adult SC, a finding that is consistent with visual experience-mediated prevention of adult plasticity (Balmer and Pallas, 2015a), but also leads us to question why DR adults have reduced GABA_A responses in SC when exposed to receptor agonists and antagonists (Carrasco et al., 2011). Several possibilities exist and are explored in Chapter 3 of this dissertation.

Sensory deprivation, such as dark rearing from birth affects the maturation of several RF properties, and can significantly reduce responses throughout the visual pathway (Teller et al., 1978; Cynader and Mitchell, 1980; Mower, 1991; Fagiolini et al., 1994; Prusky et al., 2000). One element that has been largely overlooked in this area of study is the changes in visually-dependent behaviors associated with the loss of (or reduced sensitivity of) individual response properties. Although some recent work has suggested that sensory experience is not necessary for the establishment of mature visual circuits (Kang et al., 2013a), researchers fail to account for deficits that are not expressed until later in life (>P90) when some mature circuits (such as those

for RF refinement) fail after experiencing early sensory deprivation (Carrasco et al., 2005). We compared the necessity of refined RFs in mediating the learning of and execution of two visual behaviors. We showed that refined RFs are sufficient to improve both SC-dependent looming responses, and V1-dependent visual discrimination of spatial frequency gratings. Our results suggest that early visual experience is not actually required for attaining normal (and sharpened) behavioral responses to overhead “predatory” stimuli, and reinforces the notion of refined RFs translates to improved visual acuity in adults.

My experiments reveal that early experience-dependent TrkB activity acts as a trigger, preventing the onset of maladaptive plasticity in SC in adulthood, thus allowing RFs to stabilize in a mature (refined) state. These findings, in conjunction with the established link of TrkB signaling in the development of V1 (Gianfranceschi et al., 2003), suggests a widespread role for TrkB signaling in mediating the maturation of visual circuits throughout the visual pathway. I also provide evidence supporting the conclusion that the maturation of RF size in SC improves SC-dependent visual behaviors, such as the looming response. This work should provide a foundation for future experiments studying the downstream mechanisms involved with mediating the effects of early sensory experience on the development and fine-tuning of sensory circuits in the brain.

4.1.1 BDNF/TrkB signaling in critical period plasticity

Critical period plasticity has been studied in detail for decades, but the biological factors contributing to the opening and closing of critical periods are still disputed. The excitatory-inhibitory (E/I) balance is crucial for the onset of critical periods (Hensch and Fagiolini, 2005), but much remains to be learned about how and why. If an organism fails to receive the

appropriate sensory experience during this time then it may be difficult or impossible to develop related sensory functions later in life. Functions that are critical to survival, like language, vision (Wiesel and Hubel, 1963a), hearing (Kral et al., 2002), and psychological imprinting (Lorenz, 1958), are especially dependent on environmental experience during a critical period.

There are two major premises regarding critical period plasticity in rodents: one is that the development and maturation of GABAergic inhibition are crucial for opening and closing them and second, that increases in GABAergic inhibition are dependent on the increased expression of BDNF during this time period (Hanover et al., 1999; Huang et al., 1999). In rat V1, BDNF mRNA and protein increases following eye opening, crests during the critical period (P15-P30), and remains elevated until adulthood (Castrén et al., 1992; Bozzi et al., 1995; Rossi et al., 1999; Tropea et al., 2001; Patz and Wahle, 2006), a timetable that overlaps with the maturation of GABAergic inhibition in V1 (Hensch, 2005b). Interestingly, recent evidence suggests that BDNF/TrkB signaling may in fact, reverse its effects during the critical period for V1, so that a decrease rather than an increase in TrkB activity causes an increase in GABAergic inhibition (Zhang et al., 2018). Although this phenomenon has not been studied throughout other parts of the visual system, it has been observed in brainstem nuclei during brief (2 day) windows where the rat respiratory system is at its most vulnerable point in development (Liu and Wong-Riley, 2002; Wong-Riley and Liu, 2008; Gao et al., 2011). TrkB and downstream ERK signaling also appear to play a role in regulating GABAergic synapse plasticity in cortical neurons during the transition period from GABA_AR depolarizing excitation to hyperpolarizing inhibitory signaling (Brady et al., 2018), but whether this modulator relationship exists in adulthood has not been studied.

How can our results be reconciled with previous conclusions? BDNF/TrkB activity during early critical periods appears to be essential for the persistent stability, but not the initial refinement of RFs and inhibitory circuits in both SC and V1. If experience-driven signaling during the critical period functions through increased BDNF expression, we would expect an increase, rather than the reported decrease in GABAergic signaling during the critical period (Zhang et al., 2018), although it is important to note that the studied critical period in V1 P15-P30 precedes the critical period for RF refinement that was examined in this dissertation (P33-P40). This could indicate that BDNF/TrkB signaling is first used to “prime” the visual pathway prior to the opening of the critical period for RF refinement maintenance. The decreased inhibition could simply allow for hastened excitatory synapse formation, which is then followed by the experience-dependent flourishing of inhibitory synapses to stabilize refined RFs. A species difference could also exist in the facilitation of GABAergic maturation by BDNF signaling. Although RFs initially refine and are subsequently stabilized by visual experience in both hamsters (Carrasco et al., 2005) and mice (Kang et al., 2013a), rats may have different needs. Work examining this possibility is ongoing in the Pallas lab.

4.2 Explored mechanisms of adult RF maintenance and prevention of plasticity

My dissertation work also begins to address the visual neuroscience question: how does early visual experience stabilize lateral inhibition in adulthood? As described in chapter 2, BDNF/TrkB signaling is essential for triggering the maintenance of RF refinement in SC and V1, but the exact mechanisms governing that maintenance beyond P60 are poorly understood. Excitatory synapses develop and mature earlier than inhibitory ones in rat V1 (Sutor and Luhmann, 1995), a process likely supported and enhanced by BDNF. However, the refinement

of those excitatory connections requires the development and maturation of GABAergic inhibition. GABAergic inhibition is involved with the development of orientation selectivity, direction selectivity, receptive field substructure, and ocular dominance in V1 neurons (Wolf et al., 1986; Hensch and Stryker, 2004), and is implicated in the maintenance of RF refinement in SC (Carrasco et al., 2011) and V1 (Balmer and Pallas, 2015a), making it a likely candidate for preventing adult plasticity. Studying how early sensory experience and TrkB signaling can sustain mature GABAergic inhibition into adulthood is critical for scientists to understand how maladaptive plasticity can be prevented, and how it could possibly be utilized for therapeutic purposes.

4.2.1 GABA_A receptor changes in subunit composition, trafficking, and internalization

My experiments focused on identifying the cause of the reduced functional responses we have previously observed in GABA_ARs when exposed GABA agonists and antagonists in adult DR hamster SC (Carrasco et al., 2011). One possibility for this observation was a structural change in the GABA_A receptor/channel, resulting in a reduced conductance. To identify the possible compositional changes in GABA_A receptor subunits we conducted an analysis of the transmembrane receptors present in DR hamsters and compared them against those that received light-exposure (LE) during the critical period. We find that synaptically localized GABA_ARs with an alpha1 subunit are not significantly different between our treatment groups (Mudd et al., 2019), a finding that is consistent with previous reports in our lab (Balmer and Pallas, 2015a).

We considered that if total mature GABA_AR expression was not changing, then perhaps there was a dysregulation in the developmental switch of alpha2 dominant synaptic receptors to alpha1 dominant subunits, which normally happens around the end of the critical period (Davis et

al., 2000; Jacob et al., 2008). Indeed, some reports indicate that failure in this maturational development can lead to synaptic dysregulation and result in neuronal dysfunction (Poulter et al., 1999). We find however that there was no significant difference between our treatment groups, suggesting that the phasic GABA_A alpha1 receptors are maturing normally. It appears that early visual experience-driven activity does not regulate adult plasticity by ensuring the maturation of phasic GABA_ARs.

We further examined possible differences in tonic inhibition by comparing GABA_A alpha5 receptors that are primarily specific to extrasynaptic sites. Activation of extrasynaptic GABA_ARs increases the membrane conductance restricting cellular excitability (Lee et al., 2006), the induction of synaptic plasticity (Smith, 2013; Groen et al., 2014), and dendritic integration (Groen et al., 2014). Surprisingly we found that the expression of alpha5 receptors was not significantly different, and indeed, trended higher in the dark reared animals. This result unexpected because recent studies have shown that even a brief (2 day) period of sensory deprivation (dark exposure) is sufficient to reduce tonic inhibition in juvenile (postnatal day 12-27) mouse V1 (Huang et al., 2015a). Our studies also focused on adult plasticity, rather than critical period plasticity, so the possibility exists that the reported DR induced reduction in tonic inhibition early on (P27-P40) may not persist into adulthood, but may provide enough plasticity for RFs to begin to re-enlarge. Alternatively, it could be that a different extrasynaptic GABA_AR subunit, such as delta, could be regulating tonic inhibition in SC, or that posttranslational modifications other than subunit composition could be affecting the function of GABA_ARs.

It is also possible that the significant differences in GABAergic architecture between SC and V1 result in different mechanisms governing tonic inhibition. For example, in all areas of cerebral cortex studied thus far, as well as striatum and hippocampus, parvalbumin positive (PV)

interneurons are almost entirely a subpopulation of GABAergic neurons (Gonchar et al., 2008; Klausberger and Somogyi, 2008; Tremblay et al., 2016). PV interneurons exhibit fast-spiking patterns and form immediate inhibitory synapses with the proximal dendrites, somata, and initial segments of pyramidal neurons (Kawaguchi and Kubota, 1993; Gupta et al., 2000; Markram et al., 2004; Taniguchi, 2014; Tremblay et al., 2016), thus giving them a key role in intrinsic inhibitory microcircuits in subcortical and cortical brain areas (Cardin et al., 2009; Sohal et al., 2009; Chen et al., 2017), and in mediating the onset of critical period plasticity (Fagiolini et al., 2004). In SC however, PV interneurons appear to have a number of distinct functions including projecting to thalamus, (Casagrande, 1994; Mize, 1996), the parabrachial nucleus which in turn projects to amygdala in a signaling pathway for fear responses, (Shang et al., 2015), and acting as local mediators of direct and feedforward GABAergic synaptic responses as well as excitatory glutamatergic synapses (Villalobos et al., 2018). These reports support the possibility that PV neurons in SC are specialized for a variety of circuit functions rather than forming a homogenous GABAergic interneuron subtype as they do in the rest of the brain, and provides a possible explanation for why we were unable to observe the same tonic inhibition changes observed in V1. Future experiments in the Pallas lab will be examining these possibilities.

Our final experiment regarding GABA_A receptors examined the possibility that the rate of endocytosis could be reintroducing adult plasticity by reducing the number of GABA_ARs present for reinsertion into the synaptic membrane. GABA_ARs go through regular exchanges in a constant cycle between the plasma membrane and intracellular compartments (Jacob et al., 2008; Mele et al., 2016). This exchange process regulates total cell surface expression of GABA_ARs and plays a key role in the postsynaptic receptor pool size and the overall strength of GABAergic inhibition (Mele et al., 2016). Internalization of GABA_ARs has been shown to be a

mechanism underlying the development of epilepsy (El-Hassar et al., 2007), autism spectrum disorder (Ali Rodriguez et al., 2018), and Rett syndrome (Gataullina et al., 2019). The neuronal hyperexcitability present in these disorders is theorized to occur because of a reduced rate of GABA_AR reinsertion into the membrane at the synapse (Goodkin et al., 2005). Interestingly, there are also reports of increased extracellular tonic GABA currents in cases of epilepsy (Naylor et al., 2005), suggesting that changes in the endocytosis rates of both synaptic and extrasynaptic GABA_ARs could be mediating a loss of inhibition we observe in SC in DR adults. We examined both alpha1 and alpha5 subunit expressing GABA_ARs and found that the intracellular/plasma membrane expression of both was consistent in both DR and LE adult hamster SC. These results suggest that the rates of endocytosis are not mediating the reductions in inhibition that appear to underlie the reintroduction of adult plasticity in SC following early sensory deprivation.

4.2.2 Scaffolding proteins in mediating synaptic plasticity

Having found no differences in the composition or localization of GABA_ARs, we analyzed the role played by the inhibitory synapse anchoring protein gephyrin in mediating adult maladaptive plasticity. As the most well studied post synaptic density protein for GABA_ARs, gephyrin presents a promising subject for studying the effects of synaptic clustering and loss of inhibition. Gephyrin is necessary clustering GABA_ARs at inhibitory synapses (Essrich et al., 1998; Kneussel et al., 1999; Levi et al., 2004; Jacob et al., 2005), but only for receptors possessing the alpha2 subunit. Gephyrin-independent clustering has also been reported (Zita et al., 2007), suggesting that other mechanisms likely contribute to restricting GABA_ARs at inhibitory synapses. Our study provides an opportunity to study long term changes in gephyrin expression following the onset of adult plasticity and the re-enlargement of RFs. We find that

the total expression of gephyrin throughout the cellular membrane in SC was not significantly affected by early sensory deprivation. One potential explanation for our finding is the recent discovery that total gephyrin expression may not be indicative of functional gephyrin-dependent clustering of GABA_ARs. Instead, the formation of clustered gephyrin nanodomains provides a stabilizing effect on GABAergic currents (Pennacchietti et al., 2017), providing a rationale for how total gephyrin expression may not be as important as its local organization at post synaptic sites. Future work could examine this possibility in adult SC and V1 by utilizing super resolution imaging to identify the synaptic clustering of gephyrin microdomains in adults.

We studied whether early visual experience may stabilize glutamatergic synapses in adulthood by maintaining the maturation of PSD-95 expression in SC. Despite the evidence for the crucial role of inhibition in stabilizing developing sensory circuits, recent studies have found that the maturation of excitatory synapses may play a more dominant role. The maturation of silent synapses, which involves the insertion of AMPA receptors into dormant (NMDA receptor-only) synapses by the presence of PSD-95, can account for the closure of the critical period for ocular dominance plasticity in mice without any changes in inhibitory tone (Huang et al., 2015b). By negating PSD-95 after critical period closure AMPAergic synapses were forced back into a silent state and ocular dominance plasticity reopens permanently (Huang et al., 2015b). One attractive element of this theory is that BDNF/TrkB signaling is required for silent synapse maturation to occur (Itami et al., 2003), which when taken with our findings from Chapter 2, make this a strong candidate for explaining the loss of RF refinement in adulthood. Unfortunately, our results show that PSD-95 expression was no different between DR and LE adults, suggesting that decreased expression of PSD-95 was not responsible for loss of RF maintenance in adult SC. In light of our results, it would appear that early visual deprivation

does not affect the adulthood expression of the primary scaffolding proteins governing the accumulation of excitatory (AMPA) and inhibitory (GABA) receptors at synapses in SC. Our research suggests that if inhibition is underlying loss of RF refinement, then it may be gephyrin-independent, and likely has little to do with silent synapse stability in adulthood.

4.2.3 NMDAR subunit composition changes in plasticity

We also examined the expression of NMDAR in adults to determine if dysregulation in the developmental change in the dominant NR2B/NR2A could underlie the loss of RF refinement in DR adult SC. The E/I balance represents a functional barrier which limits plasticity in adulthood (Bavelier et al., 2010a; Levelt and Hübener, 2012; Ganguly and Poo, 2013). Certain manipulations in V1, such as dark rearing, environmental enrichment, and PSD-95 KO can restore ODP in adult mice (He et al., 2006; Greifzu et al., 2014; Huang et al., 2015b), suggesting that adult plasticity is not gone, so much as it is gated. NR2A and NR2B have distinct impacts on synaptic plasticity and receptor properties (Cull-Candy et al., 2001; Paoletti et al., 2013) and could thus be a potential mechanism gating plasticity in adulthood by modulating E/I homeostasis. Our results indicated a minor (but non-significant) increase in both NR2A and NR2B expression, but no relative difference in the ratio of each receptor between DR and LE adult SC. Surprisingly, our results mirror a recent study which identified that that NR2B has no effect on plasticity restored via pharmacologically induced reductions in cortical inhibition (Liu et al., 2015). However, they also report a distinct role for NR2B in restoring ODP in adult mice by increasing glutamatergic excitation using oral magnesium treatments, suggesting that both an NR2B dependent and NR2B independent mechanism may exist for

reopening plasticity in V1. Our results suggest that early visual experience does not induce changes in NMDAR subunit expression in SC.

4.2.4 Chloride transporter pumps

We explored the possibility that changes in the intracellular Cl^- gradient in SC might account for the weaker GABA_AR responses observed in DR adults with enlarged RFs (Carrasco et al., 2011). Dysregulation of the KCC2/NKCC1 ratio has been reported in several disorders that involve loss of GABAergic signaling in adulthood, such as epilepsy (Kahle et al., 2014; Puskarjov et al., 2014), Schizophrenia (Hyde et al., 2011), Rett syndrome (Tang et al., 2016), and even ischemia (Galeffi et al., 2004; Jaenisch et al., 2010). Cl^- homeostasis regulation is essential for normal brain function.

We measured the adult expression levels of KCC2 and NKCC1 to determine if early sensory experience is necessary for the KCC2 pump to stay dominant. Irregularities in KCC2/NKCC1 ratios are indicated in several neurological disorders and are an active area of research. KCC2 KO mice display increased seizure susceptibility (Woo et al., 2002) stemming from reduced GABAergic inhibition and increase primary neuron excitability. Schizophrenia presents with a lower KCC2/NKCC1 ratio in hippocampus (Hyde et al., 2011), and a reduction in GABAergic inhibition which is correlated with visual hallucinations and cognitive delusions (Gonzalez-Burgos and Lewis, 2008). Interestingly KCC2 appears to regulate dendritic spine formation in hippocampus in a BDNF-dependent manner (Awad et al., 2018), suggesting that it may also be an effective modulator of plasticity in other brain areas. Surprisingly, we found no differences in the expression of either Cl^- pump or in their expressed ratio between DR and LE adults. Our results reveal that early sensory deprivation does not affect adult chloride pump

expression in SC and that KCC2 remains dominant and should maintain a mature Cl^- gradient across the membrane.

4.3 Clinical implications

The majority of the human brain stops producing new neurons a few weeks into embryonic development (Malik et al., 2013). Thus, any circuits formed abnormally in juvenile development, or damage acquired from injury or disease cannot be addressed by the natural regrowth/replacement of the afflicted tissues as is done for skeletal, organ, and muscle injuries. Instead, neural circuits need to be reorganized along proper developmental trajectories so that the brain can function normally.

4.3.1 Plasticity in recovery of sensory and motor function

Early in development, the brain is able to reorganize specific neuronal pathways and synapses in response to injury; however adult brains are less plastic and have only limited functional recovery potential. The maturation of GABAergic inhibitory signaling places limits on the excitability of neural circuits, and understanding how this system is maintained in adults provides insight into new therapeutic possibilities. Studies confirming the possibility of modulating GABAergic inhibition and reactivating plasticity in adulthood provide hope for possible treatments addressing brain function loss throughout life.

The visual system may be more flexible in adults than has been previously believed. Adolescents and teenagers undergoing surgical cataract removal well beyond the critical period often exhibit marked improvements to contrast sensitivity (Ostrovsky et al., 2006; Ganesh et al., 2014), suggesting that some plasticity remains in adults. Finding ways to enhance the remaining plasticity can elicit greater functional recovery in sensory circuits. Short-term inverse occlusion

and physical exercise are both effective means of boosting visual recovery (Lunghi et al., 2019) in amblyopic patients, as are video games (Li et al., 2011; Vedamurthy et al., 2015; Gambacorta et al., 2018). Our results suggest that pharmacological modulation of BDNF/TrkB signaling could also be useful in promoting V1 plasticity in adulthood by reducing inhibition. Indeed, recent reports show that intranasal BDNF administration promotes visual recovery in adult amblyopic rats (Sansevero et al., 2019).

Plasticity also aids in recovery after damage produced from events such as stroke or traumatic brain injury. Environmental enrichment has been shown to increase cortical plasticity (van Praag et al., 2000) and aid in the recovery of motor and cognitive functions following brain injury in adults (Peruzzaro et al., 2013; Bondi et al., 2014; Lajud et al., 2018). Other promising therapies such as exercise, deep brain stimulation, non-invasive brain stimulation, and cognitive training are based on increasing plasticity in the brain (Cramer et al., 2011) and could perhaps be enhanced by BDNF/TrkB signaling. In rodents a TrkB enhancer (CN2087) has been reported to be useful in reducing memory deficits and promoting complex auditory processing (Marshall et al., 2017). Even some of the therapeutic benefits in neurological recovery associated with acupuncture have been attributed to TrkB signaling (Li et al., 2017b).

4.3.2 Plasticity in GABAergic circuitry and disease

Our work has shown that visual plasticity in adult SC is likely governed by total GABA expression rather than post synaptic modifications of receptors, scaffolding proteins, or chloride pumps. Dysregulation of the GABAergic system has been implicated in several neurological disorders and our work could inform how to approach treatment for adults. Epilepsy (Kang et al., 2015; Huang et al., 2017), autism spectrum disorder (Pizzarelli and Cherubini, 2011; Howell

and Smith, 2019), Alzheimer's disease (Limon et al., 2012), Parkinson's disease (Meder et al., 2019), and Huntington's disease (Yuen et al., 2012) all report symptoms that can be traced to GABAergic dysfunction and treated with drugs targeting GABA signaling (Brichta et al., 2013; Lee et al., 2017). Anxiety disorders and depression are also linked to altered GABA function (Levinson et al., 2010; Nuss, 2015), with an increased risk of severe symptoms as the GABA system becomes less regulated at later stages in life (Kim and Yoon, 2017).

It is interesting to note that BDNF/TrkB signaling also appears to be dysregulated in psychiatric disorders (see Tejeda and Díaz-Guerra, 2017 for review). For example, decreased BDNF signaling is reported to result in the hyperpolarization of tau proteins (associated with Alzheimer's disease) (Elliott et al., 2005), with decreased full length TrkB isoform expression in post mortem patient brains (Allen et al., 1999). Treatment of disorders with BDNF has shown limited results in humans mostly due to poor blood brain barrier penetration of most neurotrophins, tissue diffusion, and a short half life of the delivered serum (Thoenen and Sendtner, 2002). New techniques to improve BDNF delivery include transplantation of BDNF-releasing cells, gene therapy with BDNF-encoding viral vectors, and nanoparticle mediated transport (reviewed in Géral et al., 2013). Exercise (Cotman and Berchtold, 2002) and monoamine based antidepressants (Hashimoto et al., 2004) are both capable of increasing endogenous BDNF production and relieve the symptoms of many neurodegenerative diseases. Small molecule TrkB agonists such as 7,8DHF have been shown to be useful in for treatment in animal models of Alzheimer's disease (Zhang et al., 2014) Parkinson's disease (Jang et al., 2010) and amyotrophic lateral sclerosis (Korkmaz et al., 2014).

It is important to note however that adult plasticity can be maladaptive, as we have shown in the destabilization of refined RFs in SC and V1 (Carrasco et al., 2011; Balmer and Pallas,

2015a). Although modulation of GABAergic inhibition and the TrkB signaling system can provide therapeutic benefits, they can also result in dysfunction. Too much BDNF can also be detrimental to learning and memory (Cunha et al., 2009), interfere with activity-dependent plasticity, and even induce epilepsy (Binder et al., 2001). Thus, caution must be taken when utilizing any means of restoring plasticity in adult brains so that well established circuits are not disrupted when attempting to treatment to impaired ones.

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