

**A TRANSIENT PERIOD FOR ENABLING MOTION VISION PRECEDES THE
CRITICAL PERIOD FOR OCULAR DOMINANCE PLASTICITY**

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Abstract

The premise that mature visual function depends upon the nature of visual experience during development is based primarily on experiments showing that visual deprivation during a ‘critical’ period early in life causes abnormalities in visual cortex and an enduring loss of spatial vision (amblyopia). There is, however, little evidence that early visual experience actually *enables* mature vision. Experiments in this thesis provide such evidence. The measurement of optomotor responses daily from eye opening permanently enhances optomotor sensitivity and the perception of visual motion. The plasticity allowing this enhancement is transient and peaks in efficacy before the start of the classical ‘critical’ period for ocular dominance plasticity. The enhancement is dependent upon optomotor responses generated by the movement of high spatial frequency visual stimuli, and is mediated by the visual cortex. These studies show that a form of experience-dependent plasticity, distinct from that of the critical period, enables mature motion vision.

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List of Abbreviations

OD = Ocular Dominance

MD = Monocular Deprivation

LGN = Lateral Geniculate Nucleus

V1 = Primary Visual Cortex

ODC = Ocular Dominance Column

dLGN = Dorsal LGN

GABA = Gamma Aminobutyric Acid

VWT = Visual Water Task

OKN = Optokinetic Nystagmus

VOS = Virtual Optomotor System (OptoMotry)

CCAC = Canadian Council on Animals Care

LE = Long-Evans

CCBN = Canadian Centre for Behavioural Neuroscience

CW = Clockwise

CCW = Counterclockwise

AOS = Accessory Optic System

DTN = Dorsal Terminal Nucleus

NOT = Nucleus of the Optic Tract

RCS = Royal College of Surgeons

VOR = Vestibular ocular reflex

NMDA = N-methyl-D-aspartate

BDNF = Brain-derived neurotrophic factor

AL = Anterolateral

Chapter 1-Introduction

A fundamental feature of the mammalian brain is its ability to change adaptively. This neural plasticity is present throughout life (Bower, 1990); however, adaptive plasticity is particularly prevalent during neural development (Knudsen, 2004). One of the clearest examples of this developmental plasticity is found in the mammalian visual system, where abnormal visual experience only during a “critical” period early in life can permanently alter the structure and function of the visual cortex (Wiesel & Hubel, 1963b). There are however, a number of unanswered questions regarding the function and timing of developmental visual cortex plasticity. For example, that the deprivation of normal experience during the critical period causes a loss of normal function has been interpreted as meaning that normal experience during a critical period *enables* normal function. However, there is no direct evidence for this interpretation; it is equally possible that deprivation in and of it self causes the loss of function. Another, is that the critical period does not begin until well after functional vision has been established at eye-opening and the purpose of this delay has not been identified. The hypothesis underlying the experiments in this thesis is that a period of enabling visual plasticity is present *before* the critical period. The results of experiments presented in this thesis will support this hypothesis by showing that transient visuomotor experience between eye-opening and the start of the critical period permanently enhances motion vision.

Chapter 1 will provide the historical background of the thesis experiments. First, the classic critical period will be introduced and discussed. This will include a description of the physiological and anatomical changes that occur in the visual system in

response to various forms of visual deprivation. Two hypothetical accounts of what is occurring in the brain between eye-opening and onset of the critical period will also be introduced. One will postulate that a “pre-critical” period exists that sets the stage for visual plasticity that is restricted to the critical period. The other will postulate that a period of plasticity distinct from that of the critical period is present.

Chapter 2 will initiate the description of experiments related to the thesis. In it, a novel behavioural task for measuring optomotor sensitivity in rats will be introduced. In addition, the optomotor thresholds of adult and developing animals will be characterized. In the course of these experiments, an experience-dependent enhancement of vision was found during the period from eye-opening to the onset of the critical period. In chapter 3, the temporal expression and experiential control of this novel period of plasticity was characterized in a series of experiments. Finally, chapter 4 will discuss the implications of this novel “critical” period for visual motion plasticity, and will provide a hypothesis for its function.

1.1 Critical period

The mammalian visual system emerged as a major model system for investigating the anatomical, physiological and behavioural substrates of developmental neural plasticity due to the pioneering work of Hubel and Wiesel in the 1960’s. They discovered that visual deprivation in frontal-eyed animals only during a “critical” period early in life could permanently alter the structure and physiology of the visual cortex. Because these alterations were accompanied by a permanent reduction of vision through the deprived eye(s) (Dews & Wiesel, 1970), understanding the nature of critical period

plasticity is thought to be a key to understanding the basis of human amblyopia (Odom, 1983).

1.1.1 Effects of monocular deprivation

Although a number of manipulations of visual experience have been used to study critical period plasticity, monocular deprivation (MD) has become the archetypal experimental manipulation because it is simple and yields reproducible results. MD involves suturing one eye shut; a treatment that dramatically reduces the amount of light entering the eye as well as information through the entire spatial frequency range. MD during the critical period causes a number of abnormalities in the visual system. Significant changes in the functioning of structures upstream of the visual cortex have not been observed following critical period MD; the physiological properties of the retina of the sutured eye (Wiesel & Hubel, 1963b; Sherman & Stone, 1973) and of cells in the lateral geniculate nucleus (LGN) both appear normal (Wiesel & Hubel, 1963b). Thus, the causes of the amblyopia cannot be attributed to deficits in visual processing between the eye and the LGN. The major alterations that occur as a result of MD are in the geniculocortical system. For example, it has been shown in cats that during normal visual experience the inputs from the LGN enter layer IV of primary visual cortex (V1) and the axonal terminals form stripes as they connect with cortical neurons (Hubel & Wiesel, 1962; Hubel & Wiesel, 1963a). These stripes are formed by the segregation of visual inputs into alternating bands dominated by either the left or the right eye to form the characteristic ocular dominance columns (ODC). It is known that these ODC's are affected by MD. Following MD during the critical period the ODC stripes corresponding

to the sutured eye are narrower than normal, whereas the stripes corresponding to the non-deprived eye are wider than normal (Hubel *et al.*, 1975). That is, input coming from the part of the LGN that relays information from the closed eye is now smaller relative to the inputs from the open eye.

The physiological properties of cells in binocular V1 are also changed, including that there is a large shift in cortical ocular dominance. OD refers to the response properties of cells in visual cortex, which can have input from one or both eyes. During visual stimulation, each cell responds preferentially to one eye or equally to both eyes. Under normal circumstances, the representation of the responses forms the characteristic ocular dominance distribution. This representation is significantly altered by MD; there is an increase in the number of cells responding to the open eye and a reduction in the number of cells responding to the closed eye (Wiesel & Hubel, 1963c; Wiesel & Hubel, 1963b; Hubel *et al.*, 1975). Stimulation of the open eye will lead to responses from an increased number of cells, meaning an OD shift toward the non-deprived eye has occurred. The alteration in the physiological properties of the cells causes the deprived eye to be virtually disconnected from the visual cortex, resulting in a loss of binocularity. Thus, the lack of normal visual experience during development results in a permanent alteration in the structure and physiology of the visual cortex (Hubel & Wiesel, 1970). As mentioned earlier, these alterations in structure and function following critical period MD are also accompanied by an enduring loss of visual acuity, termed amblyopia or *blunt vision* (Wiesel & Hubel, 1963b; Dews & Wiesel, 1970; Muir & Mitchell, 1973).

1.1.2 Effects of other alterations of form vision

Although MD during the critical period produces severe visual deficits, other, more specific, forms of visual deprivation during the critical period also have lingering effects on the visual system. For example, deprivation of specifically oriented visual stimuli produces permanent effects on orientation sensitivity. Orientation sensitivity refers to the responsiveness of cells to lines of light at a particular orientation, with each orientation being represented roughly equally throughout visual cortex. However, kittens reared during the critical period in an environment of stripes of one orientation, have abnormalities in the representation of other orientations (Blakemore & Cooper, 1970; Hirsch & Spinelli, 1970) and a reduction in the number of cells that responded to binocular inputs (Blasdel *et al.*, 1977). In addition, these animals showed behavioural deficits in detecting the orientation of lines that they were deprived of during development (Muir & Mitchell, 1975).

Specifically reducing the spatial frequency of stimuli in one eye during the critical period with a diffusing lens also results in permanent alterations in visual function. This includes severe amblyopia when measured on a grating acuity task, paralleled by a decrease in binocularly innervated neurons and a shift in ocular dominance toward the non-deprived eye (Smith *et al.*, 1980; Maguire *et al.*, 1982). Similarly, reducing the optical quality of the eye during the critical period by chronically atropinizing one eye causes a decrease in contrast sensitivity at all spatial frequencies, as well as a decrease in responsiveness of cortical cells to high spatial frequency stimulation and a shift in ocular dominance (Kiorpes *et al.*, 1987; Hendrickson *et al.*, 1987; Movshon *et al.*, 1987). These deprivations reduce the spatial frequency of the information without reducing the amount

of light entering the eye, indicating that the change in spatial frequency alone is responsible for the enduring loss of visual acuity.

Strabismus or *squint* is another form of visual deprivation that affects visual development (Hubel & Wiesel, 1965). Strabismus is the abnormal alignment of the eyes and can be induced by surgically cutting the muscles that control the movement of the eyes or by placing goggles containing prisms over the eyes so that one is deviated relative to the other. Both alterations cause cells in V1 to lose binocularity (Van Sluyters & Levitt, 1980) and result in a permanent loss of visual acuity. Strabismus does not reduce the amount of light entering the eye because the eye is not occluded, nor does it reduce the spatial frequency of the visual stimuli because the optical resolution is normal. Therefore, the OD shift that is observed is a direct result of competitive interactions based on the misalignment of the eyes.

1.1.3 Effects of motion deprivation

The deprivation of form vision during the critical period, as outlined above, has significant negative effects on visual cortex function. Visual processing for *motion* is a distinct category of visual function that is affected by visual deprivation. For example, deprivation during the critical period of specific visual stimuli moving in a specific direction, produces permanent effects on the direction selectivity of cortical neurons. Direction selectivity is the tuning of cells to respond to visual stimuli moving in a particular direction. Cats reared during the critical period in an environment containing visual stimuli moving in only one direction show an increase in the percentage of cells preferring that direction (Cynader *et al.*, 1975; Daw & Wyatt, 1976). In addition cats

raised in a stroboscopically-illuminated environment where they experience no moving stimuli have also demonstrated deficits in motion vision (Cynader *et al.*, 1976; Kennedy & Orban, 1983). Animals deprived of visual motion by a flickering strobe light had very few cells in visual cortex that were direction selective and any that were did not respond to higher stimulus velocities. The cortical cells of animals reared in a normally lit environment, have direction selectivity and respond to high velocities. These findings indicate that “motion” vision, like “form” vision, can be altered by deprivation during development. To this point, however, the effects of deprivation of visual motion on behavioural measures of motion vision have not been reported.

1.1.4 Rodents as models of visual deprivation

Although the most popular models for studying developmental visual plasticity have traditionally been cats, monkeys and ferrets, experiments using other mammals have shown that the timing of the critical period is species dependent (cats: P21-P270, Hubel & Wiesel, 1970; Daw *et al.*, 1992; ferrets: P33-P60, Issa *et al.*, 1999; mice: P19-P40, Gordon & Stryker, 1996; rats: P19-P50, Guire *et al.*, 1999). However, the effects of MD during the critical period result in similar physiological and behavioural deficits in other mammals (ferrets, Issa *et al.*, 1999; rabbits, Van Sluyters & Stewart, 1974; mice, Gordon & Stryker, 1996; rats, Fagiolini *et al.*, 1994). This similarity in effects is due in large part to the fundamental features of the visual system that are shared by most mammals.

Rodents have not been popular models of vision, in part due to the lateral position of their eyes, which makes the binocular field of vision relatively small (~40 degrees in rats; Cowey & Franzini, 1979) compared to frontal eyed animals, such as humans (~120

degrees; Wandell, 1995). In rats this laterality means ~90-97% (Grieve, 2005) of the efferents from the retina to the LGN project to the contralateral hemisphere and the binocular V1 makes up ~1/4 of primary visual cortex (Paxinos and Watson, 1998; Sefton and Dreher, 1995). In addition, the orderly arrangement of columns of neurons (ODC's), thought by some to be a fundamental organizing principle of mammalian brains, do not exist in rodents. This has lead some to conclude that rats, and rodents in general, have fundamentally different visual systems than frontal eyed animals. However, studies have shown the grey squirrel to have acuity comparable to cats even though these rodents lack the columnar organization of higher mammals (Van Hooser *et al.*, 2005). Moreover, half of the neurons in primary visual cortex of rats respond optimally to drifting stimuli rather than flashing uniform field stimuli (Girman *et al.*, 1999) and most cells (~93%) in V1 have orientation tuning; of these 59% show a directional preference. This shows that cells in V1 of these animals are highly specific and that a columnar arrangement is not necessary for visual function. Rats and mice also have several advantages over the more conventional animals used in studying vision. For example, the invention of tasks for quantifying rodent vision makes behavioural measures much easier to obtain, and MD during the critical period for both mice and rats results in amblyopia (Prusky *et al.*, 2000c; Prusky & Douglas, 2003). In addition, genetic manipulations are more inducible in rats and mice than in cats or monkeys, which may be important for identifying many of the neural substrates and molecular mechanisms of critical period plasticity. This makes rodents important and useful in examining critical periods and plasticity.

1.2 Deprivation effects versus enabling effects

In characterizing the properties of the critical period, researchers have relied primarily on deprivation studies. Though deprivation effects such as those induced by MD or orientation and direction deprivation demonstrate the negative implications of being deprived of 'normal' visual experience, they do not in and of themselves show that normal experience during a critical period enables the appropriate function. For example, it is known that MD during the critical period causes the deprived eye to be amblyopic and that this was thought to be due to an OD shift away from the deprived eye, but shifting OD back to a normal distribution does not alleviate the amblyopia (Murphy & Mitchell, 1986; Murphy & Mitchell, 1987). This implies that the deprivation is having numerous negative effects during the critical period and that a normal OD distribution does not necessarily enable normal function. An extreme interpretation of the critical period is that it has nothing to do with enabling vision, but rather, is only sensitive to deprivation effects; that is, normal visual function may be present from birth and requires no environmental stimuli to shape the neural circuits needed for normal vision. This is not likely to be the case, but inferences made about the effects of visual deprivation, say little about normal vision.

The inability of deprivation studies to fully explain how normal vision is enabled compels the use of other methods to study visual development. One alternative is to use enriched visual experience to enable vision, but few examples of this have been reported. One example of this is experiments in which enhanced acuity was found in mice reared in "enriched" housing conditions (Prusky *et al.*, 2000; Cancedda *et al.*, 2004). However, the increase in acuity was small (~18%) when compared with the large loss in acuity

produced by most rodent deprivation experiments (~40%). In addition, these studies did not restrict enrichment to the critical period, and the enhancement may simply have been the result of overcoming the deprived rearing conditions in standard cages. Though inconclusive, these experiments do provide some evidence of enabling function, but nevertheless, demonstration of this phenomenon is rare.

The lack of evidence for the enabling effect of visual function during development, may be due in part to the resolution limit set by the eyes; a value that can be estimated using the Nyquist limit (Hirsch & Curcio, 1989). This theoretical value is determined by the optics of the eye and the photoreceptor packing density. Acuity measures, dependent on visual cortex, often yield values close to the Nyquist limit and may not provide appropriate head room to observe an enabling response. For example in MD experiments, the large reduction of acuity through the deprived eye is not mirrored by an enhancement of acuity through the open eye (Prusky & Douglas, 2003), even though there is an ocular dominance shift toward this eye. That is, functional changes may be taking place in visual system circuits representing the non-deprived eye, however, resolution limits set by the eye preclude measuring these changes using behavioural methods. Therefore, to see an enabling effect on behavioural function, one would need to investigate a visual function that has capacity for a detectable increase in ability without encroaching on the Nyquist limit, and thus, eliminating this 'ceiling' effect.

The visuomotor system holds potential as a visual function that could provide the necessary head room to induce and observe a large enabling effect. Studies in cats (Grasse & Cynader, 1984), rabbits (Soodak & Simpson, 1988) and rats (Schmidt *et al.*, 1993) have shown that receptive fields of cells in the subcortical nuclei that control

optomotor responses are generally larger than those of the visual cortex, meaning these cells respond to stimuli at a lower spatial frequency than the limit of the retina and cortical neurons. Our lab recently developed an optomotor task for rodents that enables the measurement of spatial thresholds. I will show that this task can be used in rats, and that the thresholds obtained are lower than those predicted by the Nyquist limit.

1.3 Visual development preceding the critical period

Since deprivation has been shown to affect visual structure and function only during the critical period, the vast majority of vision scientists have concluded that the visual system is plastic, only during this period of time. However, the delayed start of the critical period poses a question: why does it start days or weeks (species specific) after eye-opening? Two hypotheses have been proposed to account for this long delay and will be discussed here.

1.3.1 Precritical period

One hypothesis for the late onset of the classic critical period for OD plasticity is the existence of a “precritical” period (Feller & Scanziani, 2005). This period acts as a sort of preparatory time for the plasticity that will occur and is defined as the time from when thalamic axons enter into layer 4 of V1 (before eye-opening) up to the onset of the critical period. It was previously thought that ODC’s could not be identified until the onset of the critical period (LeVay *et al.*, 1980); however more recent anatomical and physiological evidence indicates that there are functional ODC’s arising days to weeks before the beginning of the critical period (Gordon & Stryker, 1996; Crair *et al.*, 1998;

Issa *et al.*, 1999; Crair *et al.*, 2001). It is thought that this period in time is crucial to the occurrence of novel experience-dependent plasticity during the critical period.

Studies during the precritical period have primarily focused on the nature of the plasticity, specifically, activity-dependent and activity-independent ocular dominance map formation. Activity-dependent modes consist of spontaneous and visually evoked activity within the visual system during the precritical period. In mice, spontaneous retinal waves have been suggested to be crucial for normal segregation of retinogeniculate axons in the dorsal LGN (dLGN) (Grubb *et al.*, 2003), however, a distinct effect of this activity on ODC formation has not been proven. A study by Crowley and Katz (2000) on ferrets showed that neither monocular nor binocular enucleations at any time during the precritical period altered how thalamocortical axons segregated into ODC. This suggests that neither visually evoked nor spontaneous retinal activity is required for ODC formation. Although no activity-independent mode has been identified, it has been hypothesized that cells projecting from particular parts of the retina to the dLGN carry markers (Herrera *et al.*, 2003; Feldheim *et al.*, 1998) that may be conveyed to thalamocortical axons to form appropriate eye-specific segregations in the cortex (Feller & Scanziani, 2005). Conclusions drawn from studies of the precritical period suggest that it may be a time during which gross map formation occurs, while the critical period may be the time of map refinement.

The exact reason why there is a transition from a precritical period to a critical period is unknown. However, one hypothesis suggests that a transition in the level of cortical inhibition is involved. Studies using GAD65 (GABAergic enzyme contributing to GABA production) knockout mice have shown that no OD shift occurs in response to

MD, but if GABA receptor function is enhanced by a modulator such as benzodiazepine, a normal OD shift occurs (Fagiolini & Hensch, 2000). Moreover, normal mice given a benzodiazepine before the start of the critical period will trigger its onset as well as an earlier closure (Iwai *et al.*, 2003). Finally, mice with a mutated $\alpha 1$ subunit of the GABA receptor cannot have the critical period induced by benzodiazepines, suggesting the subunits importance in the transition period (Fagiolini *et al.*, 2004). Inhibition due to GABA release seems to be necessary for critical period plasticity. The cellular mechanisms as to how GABA induces the critical period remain a mystery for now. It is interesting to note that administration of GABA into V1 of aging rhesus monkeys causes the cells to have response properties similar to young animals (Leventhal *et al.*, 2003), again suggesting the importance of GABA in initiating visual plasticity.

Though the existence of a precritical period is conceivable from the research described in the preceding studies, it still may not explain why the critical period starts well after eye-opening. Because both activity-dependent and independent processes can be eliminated without having a major effect on the anatomy and physiology of visual cortex, the precritical period does not seem to be defined by cortical plasticity; rather, the changes that occur are already genetically determined. If the period from eye-opening to the onset of the critical period has any plasticity associated with it, then it must be for some other visual function.

1.3.2 Motion vision critical period

The alternative hypothesis for the existence of a delay between eye-opening and the start of the critical period is that a period of experience-dependent plasticity for a

function other than spatial vision exists during that time. Motion vision is a good candidate for this unaccounted plasticity because deprivation studies have indicated that it may have a critical period that slightly precedes the classic critical period for OD (Daw & Wyatt, 1976). In addition, motion vision is one of the fundamental processing streams between the retina and visual cortex and is conserved through the evolution of nearly all animals.

The visual perception of movement is important to a large number of species. Indeed, even organisms without vision usually have sensors to detect movement. In terms of evolutionary theory, the detection of motion plays a vital role in the survival of animals: they must be good at perceiving movement of predators and of likely prey. An inability to do this would result in disaster and it is often more important to detect immediately that something has moved rather than to know what that something is (or even in which precise direction it has moved). Sekuler (1975) proposes that:

“During evolution, motion perception was probably shaped by selective pressures that were stronger and more direct than those shaping other aspects of vision. . . . As a result of such selective pressures, our visual systems contain neural mechanisms specialized for the analysis of motion (p385).”

During development, the same theory would hold true, in that having poor perception for fine detail would not be as detrimental to survival as having poor motion perception.

My hypothesis as to why the critical period begins well after eye-opening is that this period represents a previously overlooked critical period for visual motion during which ‘normal’ visual motion experience is essential for the development of the systems necessary for the detection of moving stimuli. As was discussed earlier, studies

depriving animals of motion in all but one direction during the critical period causes a change in the electrophysiological properties of cells in V1 (Cynader *et al.*, 1975; Daw & Wyatt, 1976). Daw and Wyatt (1976) were the first to propose that the peak of the critical period for direction deprivation occurs earlier than the peak of the critical period for monocular deprivation. Using cats, littermates were matched so that one received direction deprivation while the other received monocular deprivation at 2 ½ weeks of age (Daw *et al.*, 1978). At 5 weeks of age the drum direction was reversed for the direction deprivation animals, while a reverse eye-lid suture was given to the monocular deprivation animals. Electrophysiological recordings from visual cortex were then made at some age after 4 months. The majority of cells in the monocular deprived animals were driven by the eye that was open last (i.e., open after 5 weeks). In the case of directional deprivation, the majority of the cells preferred movement in the first direction of exposure (i.e., the direction before 5 weeks of age). This indicates that the critical period for form vision must extend further into development than that for motion vision.

The development of the LGN may provide further evidence to support the existence of an early critical period for motion. In the LGN of monkeys and cats, the parvocellular layers are made up of X-like cells, while the magnocellular layers are made up of Y-like cells (Dreher *et al.*, 1976). In rodents and often in cats, these cells are referred to as beta and alpha, respectively. X-cells convey high spatial frequency information at lower temporal frequencies (fine detail; i.e., spatial vision), while Y-cells generally convey low spatial frequency information at high temporal frequencies (i.e., moving stimuli) (Lachica & Casagrande, 1988). In primates, the axonal arbors from cells in the magnocellular layer mature before axonal arbors originating in the parvocellular

layer (Lachica & Casagrande, 1988). Furthermore, during development Y arbors are smaller than adult size while X arbors are larger (Sur *et al.*, 1984). MD prevents the rapid growth of Y arbors, which in turn prevents the pruning of X arbors (Garraghty *et al.*, 1986). Thus, the development of cells conveying motion information to the cortex influences the cells for other cortical visual functions. This suggests that the critical period for direction deprivation may precede the critical period for MD effects because of the differential development of the cell types conveying the appropriate information.

Although previous work has suggested that motion vision plasticity precedes OD plasticity (Daw *et al.*, 1978), these studies were based on deprivation effects rather than normal development or enabling effects. In addition, the actual timing of this critical period for motion deprivation was not well defined and was shown to largely overlap the critical period for MD effects. Also, there was little stimulus control in these direction deprivation experiments, and enhancement effects are hard to detect because the measurements made were based on cellular recordings. For example, an enhancement effect seen through increased firing strength or synaptic efficacy may not be evident and easily distinguishable from background noise or variability in recordings. Moreover, these studies were conducted at a cellular level rather than a systems level and no behavioural studies were conducted. Even a slight change in the way cortical cells react may lead to larger changes in the behavioural output of the whole system.

A distinct form of developmental plasticity that governs motion vision may differ from that of spatial vision. Further evidence for this hypothesis is that the visual motion system appears to be relatively spared in amblyopia (Kubova *et al.*, 1996), and MD after the critical period enhances visuomotor function (Prusky *et al.*, 2005 (in preparation));

Douglas *et al.*, 2004). In addition, a reduction of visuomotor function has not been found that accompanies cellular changes resulting from MD. Based on these results, I hypothesize that developmental plasticity for motion vision precedes that for spatial vision, and that the plasticity is characterized by an experience-dependent enhancement of function following visual motion experience, rather than a reduction of function following visual deprivation.

If an enhancement of visuomotor function is present, there are several criteria that must be satisfied to identify the plastic change as an enabling effect. First, there can be no evidence of a deprivation effect, that is, there can be no decrease in visual thresholds due to early visual motion experience. Next, only one modality of vision can be affected, meaning only motion vision can show the enabling of function. Also, the effect must be large. Deprivation studies have shown large decreases in the electrophysiological properties of cells and the effects on behaviour are often severe. To be considered an enabling effect, the enhancement must be at least of the same magnitude as the changes measured in deprivation experiments. In addition, the enabling effect must be the result of only visuomotor experience. Enrichment of any other form of vision will bring into question how and why the enabling of motion vision occurred. The results of experiments in this thesis will satisfy all of these criteria.

In order to conduct these studies, a novel behavioural task called OptoMotry was employed. This task takes advantage of the optomotor response of the rat, which is used here as a model of motion vision development. The reflexive nature of the optomotor response required no training to complete the task, allowed testing from the day of eye-opening and made it possible to obtain daily measures of visuomotor thresholds in adult

and developing animals. During the characterization of the optomotor responses, an early critical period for the enabling of visuomotor function was identified. The temporal timeframe, experiential control and neural substrates of the enabling plasticity were then characterized.

Chapter 2-Characterization of the optomotor response in naive Long-Evans hooded rats

Behavioral measures of visual thresholds are critical for assessing the usefulness of genetic, pharmacological and physiological manipulations of the visual system. There has been a long tradition, dating back to Lashley and his jumping stand (1930), of devising appetitive reinforcement-based perceptual tests of vision for laboratory rodents. However, apparent limitations in the ability of these animals to learn and perform the tasks, and the time commitment necessary to generate thresholds have limited their usefulness. Another approach has been to measure the optokinetic responses of rats and mice to track stimuli rotating around animals on a mechanically controlled drum (Cowey & Franzini, 1979). Durational measures of tracking (i.e. time tracking a stimulus per minute) can be generated relatively rapidly with this methodology, but the use of mechanical control systems has made generating visuospatial thresholds (acuity and contrast sensitivity) somewhat impractical. Though these durational measures may have some value they fail to quantify the actual visuomotor capabilities of an animal. Our lab has developed highly efficient variations of both the appetitive reinforcement-based perceptual tests and optokinetic tests that can rapidly and reliably measure visual acuity and contrast sensitivity of rats. As will be shown here, each task measures a different aspect of retinal output and provides the opportunity to test each eye independently.

2.1 Visual Water Task

The Visual Water Task (VWT; Prusky *et al.*, 2000a), is a visual perception task in which rodents discriminate between two computer-generated stimuli (i.e. for spatial vision, a sinusoidal grating and a grey of the same mean luminance) (figure 1). Animals are placed into one end of a water-filled tank that has two computer monitors facing into arms at the opposite end. An invisible platform is placed just below the water's surface under the reinforced (+) stimulus and animals are rewarded for locating this stimulus by swimming to the platform and escaping from the water. Rats can readily learn salient discriminations and perform them near 100% accuracy. Spatial visual thresholds are determined by increasing the spatial frequency or lowering the contrast of a grating over trials (for an in depth task and testing description see chapter 3). Using this task it has been shown that pigmented rats have an acuity of about 1.0 c/d (Prusky *et al.*, 2000a) and a peak contrast sensitivity of 25 at a spatial frequency of 0.2 c/d (McGill *et al.*, 2004); that there are strain differences in acuity (Prusky *et al.*, 2002); that visual deprivation during the 'critical' period for ocular dominance plasticity (Gordon & Stryker, 1996; Fagiolini *et al.*, 1994) can induce amblyopia (Prusky *et al.*, 2000c; Prusky & Douglas, 2003); that enriched visual experience during development can enhance adult vision (Prusky *et al.*, 2000); and that changes in acuity can affect performance in a memory task (Prusky *et al.*, 2000b). Being non-invasive, the VWT has proved useful in longitudinal studies of intact (McGill *et al.*, 2004) and retinal-transplanted RCS rats (McGill *et al.*, 2004a). Other visual capabilities such as orientation discrimination (Bowden *et al.*, 2002), motion coherence (Neve *et al.*, 2002) and visual memory (Prusky *et al.*, 2004) have also been measured with the system. In addition to the water providing non-appetitive motivation, it

also enables the independent testing of the two eyes: The vision through one eye can be temporarily blocked, simply by placing a small cone-shaped occluder over it just before the animal is placed in the water. On land a rat would immediately remove such an occluder, but they tolerate it while swimming. This independent testing allows for within animal control.

However, the VWT has a major limitation: although it enables the efficient measurement of perceptual thresholds, it requires about two weeks to train an animal and determine a single threshold. Although, this is still faster than systems that do not use escape from the water as the motivator, the task cannot be used to study fast changing phenomena such as those that occur during early development, or during pharmacological manipulations. It is also impractical to screen large numbers of animals rapidly. Finally, young animals often lack both the cognitive and physical abilities to complete the task, making measurements through early development impossible. Consequently, a novel method to measure optomotor thresholds in rats was developed, and it is this approach that was the subject of the experiments reported in this chapter.

2.2 Optokinetic measures of vision

Optokinetic stimulation produced by rotating large drums around an animal have been utilized in a wide variety of species (cats: Evinger & Fuchs, 1978; rabbits: Fuller, 1987; human: Nieberding, 1979; monkey: Cohen *et al.*, 1973). The moving, full-field stimulus invokes slow eye and head movements in the direction of rotation, as well as a feeling of self-motion (Fuller, 1985). With prolonged rotation the compensatory slow eye movements are interrupted by quick repositioning fast phases, or saccades in the opposite

direction. The eye movements form the characteristic optokinetic nystagmus (OKN) while the less-well studied head movements are often called optomotor tracking. Although these behaviors are reflex-like and thus no training is needed to observe them reliably, they have proved much more useful in investigating the motor control aspects of the behavior than evaluating vision. This again is due in part to the inability to quantify real visual thresholds. Measuring visual thresholds with a conventional OKN drum is difficult because the stimulus pattern on a mechanical optokinetic drum is not easily changed (e.g. Coffey *et al.*, 2002; Schmucker *et al.*, 2005). Moreover, the animals must be restrained to some extent so that their eyes remain at the center of the drum (Thomas *et al.*, 2004). As has been shown in a recent report (Prusky *et al.*, 2004a), both of these disadvantages can be obviated by replacing the mechanical drum with a virtual-reality cylinder. Being computer-generated, the spatial frequency, contrast, and velocity of the stimulus pattern can be changed instantaneously. Furthermore, by monitoring the position of a freely-moving animal inside the system with a camera, the drum can be kept centered on the head. It is not necessary to restrain the animal. Using such a virtual optomotor system (VOS) with rats, an acuity and or contrast sensitivity measure can be obtained within a few minutes. This makes it practical to test larger groups of animals and in so doing, obtain behavioural visual thresholds for each animal daily.

2.3 Measurement differences between the VWT and the VOS

The VWT and the VOS do not yield completely equivalent results: the visual acuity of rats measured with the VOS is consistently lower than that measured in the VWT. As will be shown in this chapter, the lower optomotor acuities probably reflect

the properties of the retinal efferents to subcortical structures. In contrast, because visual cortex lesions and early visual deprivation both reduce acuity thresholds measured with the VWT, the VWT seems to be most sensitive to what is being conveyed by the geniculo-cortical pathways (Prusky et al, 2000c; Prusky & Douglas, 2004a).

In conducting these characterization studies on adult animals' asymmetrical tracking at the highest spatial frequencies, near the acuity threshold, was observed. That is, an animal would track reliably in one direction but not the other. Consequently, one might hypothesize that differences seen with the different directions actually reflected the different acuities of the two eyes. This is plausible as a similar pattern has been reported with optokinetic nystagmus (OKN) in which each eye drives a different direction of the slow phase eye movements (Hobbelen & Collewyn, 1971; Grusser-Cornehls & Bohm, 1988; Harvey *et al.*, 1997). Although the neural mechanisms underlying head tracking are not as well understood as they are for OKN, undoubtedly, there is a large commonality. If each eye could be tested with a different direction of visual motion without having to use occluders, suturing an eye shut, or restricting the movement of the animal, this would be very useful as it would allow within-animal controls in many experiments. It would also have implications for identifying the central pathways conveying the visual information, and hence for the retinal sources.

This study characterizes the optomotor capabilities of adult and developing Long-Evans rats. To conduct these experiments a novel task called OptoMotry is used to generate and quantify the optomotor thresholds of these animals. In addition, the experiments provide evidence that the optomotor head response is, in fact, due to activity

in crossed subcortical pathways, and that the thalamocortical pathway normally has little or no role.

Methods

Animals

The animals were housed and handled with the authorization of the Canadian Council on Animals Care (CCAC) and supervision of the animal care committee at the University of Lethbridge.

Sixteen Long-Evans (LE) hooded rats were used in this study. All rats were bred from stock originally obtained from Charles River and raised in the Canadian Centre for Behavioural Neuroscience (CCBN) vivarium. For the duration of the experiment, all animals were housed in Plexiglas cages (35cm L x 20cm W x 13cm H) in a room with an ambient temperature of 21° C, 35% relative humidity and on a 12/12 light/dark schedule. Food and water were available ad libitum. Pups used were weaned at 21 days of age, at which time the males and females were separated and housed under identical conditions.

Visual Optomotor Apparatus: OptoMotry

OptoMotry has been described in detail previously (Prusky *et al.*, 2004; Douglas *et al.*, 2005) (figure 2a). A virtual cylinder consisting of vertical sine wave gratings was projected onto four VGA computer monitors (19 in. VGA; ViewSonic E90F) arranged in a square around a testing arena made up of a Plexiglas box (46 cm L x 46 cm W x 73 cm H). A rectangular hole (36.5 cm W x 27.5 cm H) was cut into each side of the box and the computer monitors were placed against the side to project the image into the testing

arena. On the bottom of the apparatus there is a mirror reflecting up and a hole was cut in the middle through which a bolt was placed and held in position with a nut. On top of the bolt, approximately in the middle of the arena, was a Plexiglas platform that could be changed in order to accommodate different sized animals. A mirror with a large access hole (diameter, 28 cm) cut in it was placed on top of the apparatus and reflected back down into the testing arena. A hinged lid enclosed the top of the apparatus. A firewire camera (iBot; www.orangemicro.com) was placed over a hole in the center of the lid and faced down into the apparatus. The whole arena was placed on the floor in a dark, quiet room.

The virtual cylinder was projected onto the monitors (figure 2B) using a computer program (OptoMotry; CerebralMechanics, Lethbridge, Alberta, Canada) which drove video cards (ATI Radeon 7000 Mac Edition; Markham, Ontario) installed in a dual processor G4 computer (Power Macintosh; Apple Computer Corporation). The screen light levels (black mean, 0.0103 cd/m^2 ; white mean, 92.9975 cd/m^2) were measured using a light meter (model LS-110; Minolta, Osaka, Japan). The visual stimuli was projected onto the monitors and from the perspective of the platform appeared as a virtual 3D cylinder. The computer program was used to control the spatial frequency, contrast, direction and speed of the stimulus. The camera allowed an observer to view live video feedback from the testing arena onto a fifth monitor. A crosshair, controlled by the observer, was always placed over the rats head in order to keep the virtual cylinder at a constant distance from the animal, which allowed for the spatial frequency of the grating to be “clamped” (figure 2C).

Behavioural testing using OptoMotry

At the beginning of each testing session the computer program was started and the platform was centered in the apparatus. The rat was then placed on the platform and allowed to freely move. The lid of the box was shut to enclose the testing arena. The crosshair was then placed over the animals head and the sine wave grating was then turned on and rotated at a constant rotation (12 deg/sec). When a grating perceptible to the rat was projected onto the screens the animal would generally stop moving its body, plant its feet and reflexively rotate its head in the same direction and at the same approximate speed as the gratings (figure 2D). An observer watching the live video feed was able to assess whether or not the animal rotated its head in response to the moving stimulus. This was done by observing the animals head movement in response to the grating against the arms of the stationary crosshair.

If at anytime the animal jumped or slipped off the platform, the uniform grey screen was turned on and animals were placed back onto the platform. Before initial testing animals were habituated by gentle handling and placement on the platform for a few minutes. The rats were generally tested in the first few hours of the light cycle, normally for 10-40 minutes. Whenever possible, the experimenter was blind to previous results, as well as the treatment and age of the animals.

Determination of visual thresholds using OptoMotry

When measuring grating acuity, testing always began with a grey stimulus projected onto all four monitors, at which point the rat was placed on the platform and the lid was closed. The rats were generally very active for a few moments, but soon came to

be nearly still. Then the grey stimulus was replaced by a low spatial frequency (~ 0.1 c/d) sine wave grating (100% contrast) of the same mean luminance as the uniform grey stimulus and moving at a constant rotational velocity (12 deg/sec) in one direction. The behaviour of the animal was assessed for a few seconds and then the observer made a determination of head tracking, at which point the grey screen was projected back onto the screens. The spatial frequency of the gratings was adjusted using a method of limits staircase procedure. If the animal did not respond, the experimenter chose “No” and the spatial frequency automatically decreased, however, if the animal tracked the stimulus the experimenter chose “Yes” and the spatial frequency increased. The spatial frequency of the grating was increased until the rat no longer rotated its head in response to the grating stimulus. The highest spatial frequency to which the animal responded was recorded as the visual threshold. This process was then done for the other direction of rotation in the same animal and thus a value for each direction was obtained. Occasionally, during testing, sudden changes in luminance, direction of rotation, taps on the lid or squeaking noises were required to induce the animal to stop moving, thus causing the animal to look in the direction of the screens and to facilitate more rapid testing.

A contrast sensitivity function was also recorded using a similar procedure to that described above. Once a grating acuity threshold was determined, contrast threshold points were identified between 0.031 and 0.400 c/d (0.031, 0.064, 0.092, 0.103, 0.119, 0.167, 0.272, 0.400 c/d). At each spatial frequency the contrast was decreased using the same staircase method until the contrast threshold was reached. The threshold at each spatial frequency was then calculated as a Michelson contrast from the screen luminances

$(\text{maximum} - \text{minimum})/(\text{maximum} + \text{minimum})$. The contrast sensitivity (the reciprocal of the threshold) was then plotted against spatial frequency on a log-log graph.

Optomotor thresholds of Long-Evans hooded rats

Visuomotor acuity and contrast sensitivity thresholds of adult rats (N=6, ~150-270 days of age) were measured in OptoMotry (apparatus described above). For each value obtained, measurements were made on two successive days to verify the results. Upon completion of the initial optomotor characterization, the animals received temporary eye sutures (procedure described below). To determine the role of primary visual cortex in the optomotor response sequential unilateral primary visual cortex lesions (procedure described below) were done on two separate days in order to create a complete bilateral lesion (same animals as used above, N=6). Following each lesion, optomotor thresholds were measured. Another group of four adult animals were tested and then received one time bilateral primary visual cortex lesions followed by post-surgical measurements of their optomotor thresholds again until no further change occurred.

Due to the reflexive nature of the optomotor response and because the response is present from eye-opening, the visual thresholds of developing animals could be measured. To determine how the development of visuomotor function progressed, rats (N=6) were measured in OptoMotry from the day of eye-opening (P15). Pups were removed from their home cage and tested daily from P15-P30 and then periodically into adulthood. Testing commenced within two hours after eye-opening and was repeated at the same time of day for the subsequent testing sessions. Upon completion of testing

each day (approximately 30-40 minutes per animal) pups were returned to their home cage.

Eye sutures

Monocular testing was done using the classic method of briefly suturing one eye shut. Animals were anesthetized with inhaled Isoflurane (induction at 5%, maintenance at 2-4% evaporated in 1-1.5 l/min O₂). Animals were then taped down and immobilized under a dissecting microscope with the eye to be closed facing up. A topical antibacterial ophthalmic agent (Vetropolycin) was applied to the eye and the area around the eye was washed with saline and wiped with dilute Hibitane and 70% ethanol. The eye was sewn shut with a single mattress stitch (6.0 silk) placed below the eyelid margin and a significant distance from the pupil. The knot was sealed with cyanoacrylate glue and the animals were injected with an analgesic (Buprenorphine; 5 mg/kg). Animals recovered on a warm pad and were returned to their home cages once they were alert, mobile and eating and drinking. The typical procedure typically lasted approximately 5 minutes. Following testing, animals were re-anesthetized and prepared for surgery in the same way as described above and sutures were removed using forceps and iris scissors. The eyes were then flushed with sterile saline and Vetropolycin was applied to the eye and a post-surgical analgesic was administered. Control animals were treated in the same way, but sutures were not used. Acuity and contrast sensitivity was measured 1-2 hours before surgery, 1-2 hours following the eye suture and again within a couple hours following the removal of the suture.

Primary visual cortex lesions

Animals were anesthetized and maintained with inhaled Isoflurane (induction at 5%, maintenance at 2-4% evaporated in 1-1.5 l/min O₂). The animals were then placed in a stereotaxic frame and a topical antibacterial ophthalmic agent (Vetropolycin) was applied to the eyes. The top of the head was then washed with saline and wiped with dilute Hibitane and 70% ethanol. A midline incision was made and the scalp was retracted to expose the skull. A dental drill was then used to remove a rectangular portion of skull above primary visual cortex (6-12 mm posterior to bregma and 1-3 mm from the midline) as identified by Paxinos and Watson (1998). The dura was resected and the area was aspirated down to the white matter. The incision was then closed with sutures and the animals were given an analgesic (5 mg/kg Buprenorphine). More analgesic was administered as needed. Animals were allowed to recover on a warm heating pad and then returned to their home cage once they were mobile, alert and eating and drinking. In one experiment the lesion was a complete bilateral removal, while in another there was a sequential unilateral removal over a period of time resulting in a complete bilateral removal.

Post-surgical testing

All post-surgical testing was done using the optomotor task and so was not physically demanding on the animals. Testing commenced 3 days following surgery and all animals performed well without any lingering side effects aside from the expected visual deficits.

Once testing was completed, lesioned animals were sacrificed to verify the lesion location and size. The rats were anesthetized and then perfused with cold buffered saline and buffered 4% paraformaldehyde. The brains were removed and digital pictures of the dorsal surface were taken for quantification. The surface features of the brain and the lesion boundaries were then traced and fiducial landmarks were then used to estimate the borders of striate cortex according to stereotaxic coordinates (Paxinos & Watson, 1998; Sefton & Dreher, 1995), which were then superimposed on the illustration of each animal's brain.

Statistical analysis

Repeated measures analyses of variance (ANOVA) were used to examine the acuity of the rats over time throughout the course of the experiments. The probability level at which the null hypothesis was rejected is represented by p ; statistical significance was at $p < 0.05$.

Results

All the animals were able to track a perceivable stimulus at every age tested. All animals learned to remain on the platform throughout the testing session during which accurate and consistent visual thresholds were obtained.

Visuomotor thresholds of Long-Evans rats

In the initial phase of this experiment the acuity and contrast sensitivity of naïve adult animals was measured. Figure 3A compares the visuomotor acuity values with those

obtained from the VWT. The optomotor acuities (0.54 c/d; SEM=0.0026) were ~47% lower than those measured using the VWT. Long-Evans rats typically have a VWT acuity close to 1.0 c/d (Prusky *et al.*, 2000). Figure 3B shows a typical contrast sensitivity curve for Long-Evans rats using the optokinetic system. Data from McGill *et al.* (2004) are also plotted to show that the two tasks yield different contrast sensitivity curves. In the VWT the peak of the curve is at ~0.2 c/d, while in OptoMotry we find that the peak has shifted down to a lower spatial frequency of ~0.1 c/d. However, OptoMotry yields higher contrast sensitivity values than the VWT, 35 and 25 at the peaks, respectively. Contrast sensitivity in the optomotor system is shifted towards lower spatial frequencies compared to the VWT.

Dependence on direction

In figure 3, the direction of rotation was ignored, but as was previously mentioned in the optomotor task description we have the ability to control the direction of cylinder rotation. In fact, we often saw small differences in both contrast and acuity thresholds: near threshold an animal would track in one direction, but not the other. Figure 4 shows an analysis of the variability in acuity measures. There was a range of about 0.02 c/d between animals. This corresponds to a difference of 7 cycles around the whole drum. The acuities tended to be correlated such that an animal with higher than average acuity with clockwise (CW) motion would also have a high acuity when the rotation was counterclockwise (CCW). However, the acuities were rarely identical, and moreover, the differences between the directions of motion were consistent. As shown in figure 4, the average difference between the two directions measured in each animal was

approximately 2 times greater than the average difference in the same direction when measured on successive days. Thus, the difference in direction is not likely due to measurement error and is due to threshold differences between the eyes of each individual animal.

To check the relationship between the direction of rotation and each eye, one eye on the same rats used previously was sutured shut, and measured their acuity through the open eye. When the left eye was closed there was no tracking at any frequency with CW stimulus motion, and thus, we could not measure acuity (figure 5). When the motion was reversed to the CCW direction, tracking was normal and acuities were identical to those seen in the same direction when both eyes had been open. The complementary pattern happened when the right eye was closed. Thus for each eye, motion in the temporal-to-nasal direction evokes tracking, whereas, motion in the nasal-to-temporal direction does not.

Effects of cortical lesions

The role of the cortex in visuomotor thresholds was examined by making lesions of primary visual cortex. Four animals were given bilateral V1 lesions and then tested 3 days later. There was an initial small recovery over the first 3 days of testing which then leveled off at 0.523 c/d (SEM=0.0008) resulting in a small loss in visuomotor sensitivity ($F_{(1,6)}=107.556, p<0.0001$) (figure 6A). The lesions were large with most of V1 having been removed (figure 6B). To then confirm these results, sequential V1 lesions were made on six animals. Unilateral lesions of the right V1 were made first. Figure 6C shows that there was a small decrease in acuity on the day after surgery. There was some

recovery over the next two weeks to 0.535 c/d (SEM=0.003) which was slightly lower ($p<0.0001$) than pre-surgery thresholds of 0.543 c/d (SEM=0.006). This was true whether the motion was driving the tracking through the ipsilateral or contralateral eye: both directions were basically unaffected. Removing the left VI six days later, to make the combined lesion bilateral, again had only a very small effect dropping the acuities down to 0.522 c/d (SEM=0.004) ($F_{(12,130)}=13.3, p<0.0001$). As can be seen from the superimposed brain traces (figure 6D), the cortical lesions were large, with most of primary visual cortex being removed, however, some lesions also extended into extrastriate areas.

Development of the optomotor response

The visuomotor sensitivity of rats on P15 was 0.261 c/d (SEM=0.006) and increased ($F_{(19,100)}=5383.823, p<0.0001$) until P25 at which point thresholds leveled out and did not change after P27 into adulthood (figure 7A). Acuity reached a final adult value of 0.865 c/d (SEM=0.00138). The contrast sensitivity also changed with the peak of the curve at 0.103 c/d increasing from 5.024 (SEM=0.149) on P15 to 33.567 (SEM=0.605) in adulthood (figure 7B). The contrast sensitivity curve measured as adults was similar to naïve animals (reported previously in figure 3B); however, the points after the peak of the curve did differ with the developmental group having lower values. Contrast sensitivity of each spatial frequency channel (see Appendix A) increased until about the same age, but the development of each one was slightly different with some of them being grouped into “families” based on profile similarity.

Summary

These results demonstrate that the virtual optokinetic system works well for assessing visuomotor thresholds in rats. It provides a pure measure of the capability of subcortical retinal efferents, and independent testing of the two eyes is possible simply by controlling the direction of rotation. This task can also be used to test animals from eye-opening; however, the optomotor thresholds obtained from these animals differ from experimentally naïve animals measured as adults. This finding warrants further examination and will be discussed in detail in chapter 3.

Eye-specific tests

The complete asymmetry in tracking allows independent testing of the two eyes. Because only temporal-to-nasal motion was effective through each eye (figure 5), CW movement will drive the tracking through the left eye and CCW motion will drive tracking through the right eye. This has also been reported by Thomas *et al.* (2004), and is not surprising, if as is argued below, the behaviour is solely due to crossed subcortical projections from the eyes. A similar pattern has been seen in optokinetic eye movements in rabbits (Hobbelen & Collewijn, 1971) and rats (Harvey *et al.*, 1997). The usefulness of this asymmetry is hard to overestimate as it facilitates experiments in which one eye is treated and then compared with the other eye in the same animal. Such within-animal controls are powerful as they will allow manipulations in one eye or one hemisphere of the brain to be directly compared to the opposite side of the animal. These comparisons will be free of many of the confounding variables that often accompany research involving control animals.

Role of the cortex

Cortical lesions had no effect on optomotor thresholds suggesting that the acuity and contrast thresholds reflect the properties of retinal afferents to subcortical structures like the Accessory Optic System (AOS). Cortical lesions also have no effect on OKN eye movements (Hobbelen & Collewijn, 1971; Harvey *et al.*, 1997), again suggesting the two components of gaze stabilization share a common pathway. There is anatomical and physiological evidence in rats for cortical projections to the AOS (Takada *et al.*, 1987; Giolli *et al.*, 1988; Schmidt *et al.*, 1993), but these do not seem to be necessary for producing the thresholds measured from our rats. In cats and monkeys, OKN is seen in both directions with monocular viewing conditions, and cortical lesions abolish the ipsilateral tracking. Thus, while there is a small ipsilateral projection in rats from each eye to the cortex, it does not seem sufficient to confer binocularity to the rat optokinetic system.

If the cortex plays no role in the visual tracking in our task, then the question arises as to what the cortical projections to the AOS do. Miles (1998) has proposed that the cortical pathway is primarily there to cope with translational movements that change the distance to an attended optic flow field. From this point of view, the rotational stimuli used here are not those that would engage the cortical pathway. This is especially true given the practice of keeping the virtual cylinder centered on the head. Here a model is proposed (figure 8) in which efferents from each eye project to the visual cortex and the AOS, but cortical projections to the AOS do not contribute to the visuomotor response. Rather the response is mediated solely by the direct projections from the retina to the AOS and on to motor nuclei.

Visual pathways

The term "acuity" has been used to refer to the maximum spatial frequency that evoked an optomotor response. The values so obtained are lower than those seen in rats in the Visual Water Task (VWT). It is unlikely that this is because the optomotor task is inherently less sensitive. As shown in figure 3B, the estimates of contrast sensitivities using VOS were equal to or higher than those we have measured previously using the VWT (McGill *et al.*, 2004). The contrast sensitivities were also shifted toward the lower frequencies. While in part this is due to the VWT not being able to display a sufficient number of grating cycles at the lowest frequencies, the shift may reflect an overall lower spatial frequency bandwidth for the circuitry driving the optomotor responses. This is consistent with the notion that the head-tracking is driven by the same subcortical visual pathways as optokinetic eye movements. The Nucleus of the Optic Track (NOT) and the Dorsal Terminal Nucleus (DTN) of the AOS are the nuclei concerned with horizontal tracking (Schiff *et al.*, 1988; Hoffmann, 1989; Ilg & Hoffmann, 1996). The spatial frequency tuning of cells in these nuclei have not been determined, but they have large receptive fields, etc (Hoffmann & Distler 1989), which is consistent with a lower spatial frequency preference. This suggests that while the VOS accurately measures the visual capabilities of the direct subcortical afferents, it may not be sensitive enough to detect small decreases in acuity of the eye. A one diopter blur, for example, might not be detectable. However, results from our lab have shown that the acuities measured in dystrophic Royal College of Surgeons (RCS) rats with degenerating retinas, decrease in a similar way in the VOS compared to the VWT (McGill *et al.*, 2005). This indicates that the VOS is able to detect small changes in acuity of the eye. For now, the VWT is

probably the best option for testing the highest spatial frequencies, but ways of engaging the cortical circuitry to be able to test the higher spatial frequencies in the VOS are being explored (Douglas *et al.*, 2004).

Chapter 3-Characterization of a critical period for visuomotor sensitivity

3.1 Behavioural measures of visual development

Determining visual thresholds in animals using behavioural measures has proven difficult. This is particularly true in rodents because they develop rapidly and at younger ages, they lack the cognitive faculties necessary to complete many of the tasks used. With that said, the visuomotor task that was described in the previous chapter was developed, in part, to allow for the quantitative characterization of rodent vision during development. This task takes advantage of a reflexive optomotor response and requires no training; that is, even developing animals have an observable optomotor response, regardless of their level of cognition. Thus, optomotor sensitivity and contrast sensitivity can be tested from the day of eye-opening and any day thereafter. Equally important to being able to measure thresholds in young animals is the ability to obtain acuity and contrast sensitivity measurements on sequential days, allowing one to detect developmental changes on a daily basis in a rapidly changing animal. As mentioned in the previous chapter, this has been one of the limitations of the VWT, in which the earliest threshold ever obtained was at P30 and at least a week is needed to obtain another threshold (McGill *et al.*, 2004). With the visuomotor task one can now rapidly measure visual thresholds each day from eye-opening (Prusky *et al.*, 2004). This daily testing will allow one to detect minor changes in thresholds from day-to-day, making it very effective at quantifying visual thresholds during development.

The inability to measure vision behaviourally in developing animals has left the question unanswered as to why the classic critical period for ocular dominance plasticity

does not begin until P21 (Fagiolini *et al.*, 1994). As was discussed previously, some have hypothesized that this is a pre-critical period, in which the brain prepares for the upcoming OD critical period (Feller & Scanziani, 2005; Crowley & Katz, 2002; Crair *et al.*, 2001). There is substantial evidence for this argument, however, it does not rule out the possibility of there being a period that is important for the development of some other visual function.

A finding that supports the theory of having multiple critical periods comes from experiments manipulating visual motion. Daw and colleagues have identified a critical period for directional deprivation that overlaps the critical period for monocular deprivation (Daw & Wyatt, 1976; Berman & Daw, 1977; Daw *et al.*, 1978). These two incidences of plasticity are similar, but the critical period for directional deprivation occurs slightly before the period for monocular deprivation. This finding provides the most compelling evidence for the argument that there may be a critical period for visual motion that precedes the classic critical period of ocular dominance. However, the lack of stimulus control in these direction deprivation experiments poses some questions. For example, can an enhancement effect rather than a deprivation effect be induced under the appropriate circumstances? After characterizing the development of the optomotor response in the previous chapter, it was obvious that animals tested in OptoMotry from eye-opening had higher optomotor sensitivities than naïve adult animals. This finding indicates that a critical period for visuomotor function exists before the onset of the classic critical period, and that this visuomotor critical period is characterized by an enhancement, rather than a loss of function. Another question then arises: what aspect of visual motion is altered, that is, does the critical period for motion plasticity apply to both

visuomotor and perceptual function? In this chapter we characterize the visuomotor critical period and show this to also be a critical period for perceptual motion vision.

3.2 Neural substrates

The neural substrates that underlie the enhancement of visuomotor function were unknown and required investigation. Plasticity for the increase in visuomotor acuity is likely limited to either the AOS or the cortex. As was described previously, the cortex does have connections to the subcortical nuclei (Takada *et al.*, 1987; Giolli *et al.*, 1988; Schmidt *et al.*, 1993); however, results in the previous chapter indicate that this connection does not contribute to the visuomotor responses of naïve adult animals. In terms of plasticity in the subcortical nuclei, studies have shown that the DTN of cats reared in the dark respond preferentially to slower velocities of movement, and the OD distribution of the DTN and the NOT is almost completely monocular (Grasse & Cynader, 1986; Sengpiel *et al.*, 1990). However, these changes in the response properties of the nuclei involved in the optomotor response may not be due to direct input from the retina, rather the cortical input onto these nuclei may alter their electrophysiological properties (Grasse *et al.*, 1984). This is supported by the fact that decortications in cats have essentially the same effects on the optomotor nuclei as dark rearing and monocular deprivation (Grasse & Cynader, 1987). The experiments described above suggest that the cortex is the structure where most of the plasticity occurs and then has downstream effects through the connection with the subcortical nuclei. Though this work was done in cats, which are known to require cortical input onto the subcortical optomotor nuclei, giving rats moving stimuli experience may make the cortico-subcortical pathway

necessary in these animals, also. As will be shown here, removal of VI in rats tested from eye-opening will have an effect on optomotor tracking in much the same way that VI lesions affect OKN in cats and primates.

3.3 Stimulus control

In measuring the optomotor response, one is measuring the motor output of the behaviour based on sensory input. Rather than quantifying visual thresholds, most studies using the optokinetic drum have quantified OKN in terms of velocity (Fuller, 1987) or VOR gain (Haddad *et al.*, 1980). This has made OKN and head tracking tasks more useful at measuring the motor component of the behaviour rather than vision. Thus, an optomotor enhancement in acuity may only be an enhancement in the motor output, with no change in the receptive field properties of cells receiving sensory input through vision. The inability to have a high degree of control over the stimulus in previous experiments makes it difficult to determine visual capabilities and is partly responsible for motor function being the focus of most of the previous research. In OptoMotry, the ability to control all aspects of the stimulus allows one to quantify the motor aspect of the head tracking response (i.e., time tracking), but more importantly the control allows for the characterization of actual visual threshold (i.e., optomotor sensitivity). The stimulus control in OptoMotry will allow one to determine what behaviour is being enhanced in animals tested from eye-opening; that is, the motor output may simply be more responsive, with no increase in sensory function, or there may be an increase in the visuomotor thresholds as a result of increased experience.

3.4 Perception of visual motion

From the previous research discussed, it seems unlikely that the plasticity for visuomotor function takes place in the subcortical nuclei that control the head tracking response. It is more plausible that this plasticity takes place in the visual cortex, a structure that is known to possess the ability to undergo remarkable adaptive changes. The cortical projection to the AOS may be activated resulting in information being sent from the cortex to the AOS, or alternatively, the cortex itself may undergo changes that lead to enhanced motion perception abilities. In rats, it is known that cells in the cortex are highly orientation selective (~93%), and of these, more than half are either direction specific or preferential (Girman *et al.*, 1999). This makes rats good at perceiving moving stimuli. Moreover, it has been shown that deprivation during the critical period can affect the response properties of cells responding to visual motion (Cynader *et al.*, 1975; Daw & Wyatt, 1976). Knowing that the visual cortex possesses such motion processing abilities and that the most probable origin of plasticity lies in the cortex, it is likely that an enhancement in visuomotor function is accompanied and even caused by an enhancement in motion perception. That is, the visuomotor enhancement may be the result of an enhancement in motion perception at the level of the cortex due to an alteration in the receptive field properties of cortical cells sensitive to visual motion. This change in cortical function may then have downstream effects on the visuomotor nuclei, resulting in an enhancement of visual motion function as a whole.

The rationale for this work is that the characterization of visuomotor thresholds in developing animals (previous chapter) provided the first daily behavioural measures of vision in rats. Thresholds from animals measured daily from eye-opening were found to

be higher than experimentally naïve animals not tested until adulthood. From these results we have hypothesized that a critical period for motion vision precedes the “classic critical period” for plasticity as a result of visual deprivation. Moreover, this plasticity is characterized by an enhancement of function through increased experience rather than a loss of function by deprivation. The new critical period was characterized using two behavioural tasks to test visual thresholds in visuomotor and perceptual paradigms. In doing so, we characterized a period of plasticity for visual motion and identified some of the neural substrates necessary for the development enhancement observed in animals tested daily from eye-opening in OptoMotry.

Methods

Animals

Animals were housed and handled with the authorization of the Canadian Council on Animals Care (CCAC) and supervision of the animal care committee at the University of Lethbridge.

Seventy-two Long-Evans hooded rats were used in these studies. All rats were bred from stock originally obtained from Charles River and raised in the Canadian Centre for Behavioural Neuroscience vivarium. Animals were housed in Plexiglas cages (35cm L x 20cm W x 13cm H) in a room with an ambient temperature of 21° C, 35% relative humidity and on a 12/12 light/dark schedule. Food and water were available ad libitum. Pups used were weaned at 21 days of age, at which time the males and females were separated and housed under identical conditions.

Experiments in this chapter used the same basic techniques that were described in chapter 2 to quantify the optomotor thresholds of animals in OptoMotry. However, the experiments that will be described in the following required some small procedural alterations. Also included is a description of the VWT and experiments utilizing this behavioural apparatus.

Visuomotor thresholds of developing animals: Within-litter testing

To determine how the development of visuomotor function progressed, rats were measured in OptoMotry either from the day of eye-opening (P15, N=6), from P25 (N=6) or on single days between P15 and P25 (N=4 on each day). Pups were removed from their home cages daily and tested. Upon eye-opening, testing commenced within two hours and was repeated at the same time of day for the subsequent testing sessions. After completion of testing each day (approximately 30-40 minutes per animal) rat pups were returned to their home cages.

The effect of visual cortex lesions on the optomotor response

The effect of primary visual cortex lesions on animals tested daily from eye-opening (P15) was determined. Animals (N=4) with enhanced acuities (~ 0.86 c/d; compared to experimentally naïve animals reported in previous chapter, ~ 0.54 c/d) received bilateral V1 lesions as adults. Experimentally naïve adult animals (N=4) that were not enhanced also received bilateral lesions (chapter 2, figure 6A). In addition, the effect of unilateral lesions done in a sequential manner was also investigated. Adult animals (N=5) that were tested in OptoMotry from eye-opening into adulthood were

lesioned (animals tested from P15 in chapter 2). V1 lesions of the right hemisphere were followed by optomotor testing. Subsequent lesions of left V1 were then done and followed by optomotor testing. This methodology was similar to that done in chapter 2 on naïve animals (figure 6B).

To determine the effect that lesions would have on the development of the optomotor response, rat pups (N=11) received bilateral V1 lesion the day before eye-opening (P14). To control for the effect of visuomotor testing from P15-P25, some animals (N=6) began testing the day after the lesion when they opened their eyes (P15), while the other lesioned animals (N=5) did not begin until P25. All animals were tested until P30.

Aspirate V1 lesions

Animals were anesthetized and maintained with inhaled Isoflurane (induction at 5%, maintenance at 2-4% evaporated in 1-1.5 l/min O₂). The animals were then placed in a stereotaxic frame and a topical antibacterial ophthalmic agent (Vetropolycin) was applied to the eyes. The top of the head was then washed with saline and wiped with dilute Hibitane and 70% ethanol. A midline incision was made and the scalp was retracted to expose the skull. A dental drill was then used to remove a rectangular portion of skull above primary visual cortex (6-12 mm posterior to bregma and 1-3 mm from the midline) as identified by Paxinos and Watson (2000). The dura was resected and the area was aspirated down to the white matter. The incision was then closed with sutures and the animals were given an analgesic (5 mg/kg Buprenorphine). Animals were allowed to recover on a warm heating pad and then returned to their home cage once they

were mobile, alert and eating and drinking. Depending on the experiment, the lesion was either a bilateral lesion or sequential unilateral lesion first done on the right side of the brain and upon completion of the testing the surgery was repeated for the left side of the brain.

Post-surgical testing

All post-surgical testing was done using the optomotor task and was not physically demanding on the animals. Testing commenced 3 days following surgery in adult animals and the day after in young animals. All animals performed well without any lingering side effects aside from the obvious visual deficits.

Once testing was completed, lesioned animals were sacrificed to verify the lesion location and size. Rats were anesthetized and then perfused with cold buffered saline and buffered 4% paraformaldehyde. The brains were removed and digital pictures of the dorsal surface were taken for quantification. The surface features of the brain and the lesion boundaries were then traced and fiducial landmarks were then used to estimate the borders of striate cortex according to stereotaxic coordinates (Paxinos and Watson, 1998; Sefton and Dreher, 1995), which were then superimposed on the illustration of each animal's brain.

Experiential control of enhancement

First, it was investigated if experiencing moving gratings was required to produce the visuomotor enhancement or if exposure to the task and a static stimulus produced the same effect. Animals (N=8) were tested from the day of eye opening (P15). An animal

was placed in the apparatus and optomotor thresholds were measured in the normal manner with moving gratings. A computer program recorded all of the commands that it was given by the experimenter (i.e., change in spatial frequency or direction, grey screen, etc.). Following the characterization, a yoke control animal of the same age and litter was placed in the apparatus. The previous stimuli were then played back to the animal. Yoked animals were shown the same gratings, grey screens and other stimuli in the exact same order and time scale as the previous animal, however, the gratings were not moving. This procedure was done everyday until P25 at which time optomotor sensitivity and contrast sensitivity was measured in the usual manner until P30.

Then, the spatial frequency necessary to produce an optomotor enhancement was determined. First, animals (N=4) were exposed to a low spatial frequency grating from the day of eye-opening until P25 and then tested in the normal manner until P30. Animals were placed in the task and a moving grating of 0.031 c/d was projected on the monitors. This spatial frequency was chosen to provide enough sine waves on each screen and because it is the lowest contrast sensitivity point we measure in the contrast sensitivity function. In a complementary experiment, animals (N=4) were exposed to a high spatial frequency stimulus from the day of eye-opening and then tested in the normal manner until P30. The spatial frequency used was 0.831 c/d, which was slightly lower than the optomotor sensitivity measured in optomotor enhanced animals. During the exposure period (P15-P24) a testing session lasted 25-30 minutes for both groups, a duration similar to normal animals tested in the usual manner.

Then, an experiment similar to the one performed by Daw and Wyatt (1976) was completed; we evaluated the effect of testing rats in one direction. In chapter 2 it was

shown that only temporal-to-nasal motion relative to an eye will stimulate an optomotor response, thus allowing for within animal controls. Therefore, animals (N=4) were tested from the day of eye opening, but only one direction was used (2 in the CW direction and 2 in the CCW direction). Animals were tested until P25 and then optomotor thresholds in both directions were measured everyday until P30. Thresholds were tested twice per session as to control for the amount of time in the apparatus.

Testing visual perception using the Visual Water Task

To test the effect that early optomotor experience has on visual perception, the VWT was used. Rats were tested in OptoMotry (from P15, N=6 or from P25, N=6) until P30 and then began training in the VWT at P40.

The Visual Water Task

The Visual Water Task (Prusky *et al.*, 2000) (figure 1) consists of a trapezoidal-shaped (140 cm L x 80 cm W x 25 cm W x 55 cm H) tank filled with tap water (22 °C) to a depth of 15 cm. The 80 cm end of the pool is made of transparent Plexiglas while the rest of the pool consists of stainless steel. Extending out 46 cm from the transparent end is a midline barrier (40 cm H), which creates a Y-maze shape. Placed at the end of one arm is a submersed Plexiglas platform (37 cm L x 13 cm W x 14 cm H). From the viewing position of the animal the platform can not be seen. Two computer monitors (17 in.VGA; ViewSonic E70F) sit side-by-side at the transparent end, each facing into one arm of the pool. The water level is located at the bottom of the viewable area of the screens. Light levels (black mean, 0.0445 cd/m²; white mean, 55.35 cd/m²) were taken

using a light meter (model LS-110; Minolta, Osaka, Japan) positioned at the end of the barrier. The monitors are controlled by a PCI video card (RADEON 7000 MAC Edition; Markham, Ontario) installed in an Apple Macintosh computer (PowerPC G4; 400 MHz). The gamma response is measured (Monitor Spyder, OptiCAL; ColorVision) for each monitor and is used to linearize the video output to the screens. A computer program (Vista[®]; CerebralMechanics, Lethbridge, Alberta, Canada) was used to generate and control the stimuli, as well as record the results of each trial by input from the observer through a remote control box. A positive stimulus (+; reinforced by escape from the water) was displayed on one screen and a negative stimulus (-; non-reinforced by not escaping from the water) was displayed on the other. The hidden platform was always located underneath the screened with the + stimulus.

Training and behavioural testing using the Visual Water Task

This task takes advantage of the rat's natural ability to swim and their instinctive response to escape from water. Escape is paired with the platform that is placed directly under the + stimulus. The divider in the pool serves as the choice point and sets the spatial frequency for the animals to view.

At the start of training, a full-length divider was placed in the pool so that animals could swim on only in one side of the pool, the end of which had the escape platform associated with the + stimulus. For the four experiments completed in this study the + stimulus changed each time, but the animals were effectively able to discriminate it from the – stimulus. The animals were released in the pool from the narrow end and became effective swimmers over a couple of trials by swimming to the stimulus end of the pool.

It was also important for them to know they could escape and to swim in that general direction. Next, a short barrier (23 cm) was put in place and the animals now had to discriminate between the + and – stimuli both of the same mean luminance. The location of the correct stimulus was alternated between the left (L) and right (R) screen in order to associate the correct stimulus with the escape platform. A correct response occurred only if the animals swam into the arm of the maze that contained the + stimulus and climbed onto the escape platform; an incorrect response occurred if the animals swam into the arm containing the - stimulus. Once animals performed near perfectly on the task (90% correct or better), a 46 cm barrier was put in place and training continued. At this point, the alternating stimulus side of L and R was replaced with a LRLRLRR sequence, which we have found that rats are unable to memorize. This process was done until the animals could complete the task to near perfection (90% correct or better over at least 30-40 trials).

Determination of visual thresholds using the Visual Water Task

In the first phase of the experiment, animals were trained to distinguish a sine-wave grating from grey (figure 14A). A low spatial frequency (0.100 c/d), vertical sine wave grating (+ stimulus; 100% contrast) was displayed on one monitor and a uniform grey (- stimulus) of the same mean luminance was displayed on the other monitor. A method-of-limits procedure was used to test the threshold by incrementally changing the spatial frequency of the sine wave gratings within a block of trials until the animals performance fell below our 70% performance criterion. On each trial, if the animal made a correct choice, then the spatial frequency was increased by one cycle, a procedure

which was repeated through the low spatial frequencies, thus minimizing the number of trials away from the threshold. If the animal made an incorrect choice then a test ensued in which the animal had to get 3 trials correct in a row or 7 out of a block of 10. This procedure lasted about $\frac{1}{2}$ way through the projected range to threshold. Then until about $\frac{3}{4}$ the way through, the number of correct trials needed to advance went to 3 in a row and then 5 until threshold and if the animal got one wrong in either case they had to get 5 in a row correct or 7 out of 10. An initial threshold was found, but to verify this and also to increase the number of trials, the spatial frequency was decreased 3-4 steps (i.e., one step is equal to a block of trials at one spatial frequency) and the experimental procedure was repeated. The performance at each spatial frequency was averaged and a frequency-of-seeing curve was plotted for each animal. The point at which the curve intersected 70% was reported as the grating acuity for the animal. All rats were run as a group completing 10-20 trials per session, which lasted 30-60 minutes. No more than two sessions occurred daily and were separated by at least 1 hour. All testing was done in a dark room.

Next, animals were trained to discriminate between two identical sine wave gratings (100% contrast) of the same mean luminance, moving in the opposite direction of one another (figure 14C) at $12^\circ/\text{sec}$. Rats were trained so that the rightward moving grating was the + stimulus and leftward was the – stimulus. With the exception of the change in stimulus, the animals completed all aspects of training in exactly the same manner as was already described. Due to the previous training, only 40-60 trials were required to perform the task to near perfection, at which point thresholds could be measured. During the testing phase the spatial frequency of both screens remained

identical; therefore they were increased and decreased exactly the same amount depending on the outcome of a trial. The testing procedure and criterion remained the same as in the previous experiment and frequency-of-seeing curves were again generated.

The following two experiments relied on the same basic procedures described in the previous two experiments; however, the stimulus was changed from sine wave gratings to dots. First, dot coherence thresholds were measured. Dot kinematograms, consisting of looping 24 frame movies, were computed separately for each monitor before each trial, and then played continuously until the end of a trial. Each frame had 62 randomly positioned white dots that covered about 20% of the screen. The dots were 2.3° in diameter, a size that previous research in our lab confirmed was readily visible, and had a luminance of 90 cd/m^2 (background was 2 cd/m^2). Dots could move in random directions with a step size of 2.0° , a frame duration of 35 ms, and a lifetime of 424 ms. The dots were projected on both screens and moved in opposite directions (figure 15A). Due to the previous training the rightward stimulus was again the + stimulus. Animals began at 100% coherence, which was decreased on successful trials using the same method of limits described above. Dots on each screen began moving in the same direction, but over trials the proportion of dots moving horizontal was reduced so that most moved in random directions.

In an alteration to the dot coherence experiment, dot size thresholds were measured. 2.3° dots, moving with 100% coherence, with a step size of 2.0° , a frame duration of 35 ms, and a lifetime of 424 ms were used. Animals were trained to discriminate between dots moving to the right (+) and dots moving to the left (-), with high accuracy (figure 15C). The size of the dots was then reduced, again using the

method of limits procedure, until the minimum dot size at which animals could discriminate the direction of motion at 70% accuracy, was identified. In both dot experiments, rats only required 40-60 trials in the training phase to be able to begin testing.

Statistical analysis

Repeated measures analyses of variance (ANOVA) were used to examine the acuity of the rats over time throughout the course of the experiments. Student's *t*-test was used to compare VWT thresholds between animals with or without an optomotor enhancement. The probability level at which the null hypothesis was rejected is represented by *p*; statistical significance was at $p < 0.05$.

Results

Within-litter visuomotor experience versus naïve animals

After characterizing the developmental group (chapter 2), it became evident that animals tested from eye-opening had much higher acuities than experimentally naïve animals. Based on this evidence a within-litter study was done: half the litter was tested from eye-opening (P15) while the other half began testing at P25. Acuity of animals tested from P15 significantly increased ($F_{(15,80)}=5004.741, p < 0.0001$) to an enhanced level by P25 and plateaued at 0.843 c/d as adults (figure 9A). P25 was chosen as the age to begin testing the control animals because that was the point at which the acuity of the initial development group had leveled out. Animals that began testing on P25 had acuities of 0.531 c/d (SEM=0.001), which changed slightly ($F_{(5,30)}=7.364, p=0.0001$) the

next day, but then remained unchanged until P30 (figure 9A). The animals tested from eye-opening had significantly enhanced acuities ($F_{(1,60)}=47916.622, p<0.0001$) relative to the P25 animals, which did not differ ($t_{(5)}=-1.814, p=0.1295$) from the adult animals discussed in chapter 2 (figures 3 and 5).

There was also a significant difference in contrast sensitivity between the P15 and P25 groups ($F_{(1,80)}=342.375, p<0.0001$) when compared as adults (figure 9B), however, it was far less pronounced than observed for acuity. Upon inspection of the contrast sensitivity curves for the two groups the points up to and including the peak (0.031, 0.064, 0.092 and 0.103 c/d) appeared similar while the points after (0.119, 0.167, 0.272 and 0.400 c/d) appeared to be different. Statistical analysis revealed that there was no difference ($F_{(1,40)}=0.415, p=0.5233$) at spatial frequencies below the peak or at it, however, sensitivities at spatial frequencies above the peak were significantly lower for the P15 group ($F_{(1,40)}=2683.221, p<0.0001$), with the P15 animals having lower values at all points.

Visuomotor critical period plasticity

Using P25 as the cutoff for the visuomotor plasticity that has been described, the effect of only one day of testing was determined. After one initial day of visuomotor testing (either P15, 17, 18, 19, 20, 21, 23), animals were retested everyday from P25-P30. Animals exposed to the stimulus once all had significantly enhanced acuities over animals that were not tested for the first time until P25 (figure 10) ($F_{(9,36)}=2448.709, p<0.0001$). Acuity at every age tested, except for P23 ($p=0.1648$), was significantly higher than naïve adult animals. The acuity of animals not tested until P25 and adults did

not differ ($p=0.0552$). All values were lower than those for 'normal' enhanced animals. Visuomotor sensitivity peaked in animals tested on P19 and the curve for all days was skewed towards younger animals with almost all of the plasticity over by P23.

Effect of cortical lesions on optomotor enhancement

Following bilateral lesions the optomotor sensitivity of animals tested from P15 dropped from 0.855 c/d (SEM=0.00087) to 0.500 c/d (SEM=0.0031) 3 days after surgery and there was a slight recovery over the next 2 weeks to 0.511 c/d (SEM=0.0015; $F_{(6,42)}=7399.88, p<0.0001$) (figure 11A). The acuity of naïve animals following bilateral lesions was virtually unchanged (chapter 2; figure 6A). All values for bilateral lesions were significantly different from one another ($F_{(3,12)}=23934.14, p<0.0001$), but the only large effect occurred in the enhanced group where removing the cortex resulted in thresholds similar to those of naïve animals.

Animals used in the initial developmental characterization study (figure 8) described earlier in this chapter were used for the sequential removal of V1 in adult animals. The pre-lesion acuity of these animals was 0.865 c/d (SEM=0.0014) in the CW direction and 0.863 c/d (SEM=0.00074) in the CCW direction (figure 11C). Removal of right hemisphere V1 initially brought the CW and CCW direction down to 0.187 c/d (SEM=0.030) and 0.335 c/d (SEM=0.015), respectively. This was followed by a partial recovery of function over the next 7 weeks to values of 0.624 c/d (SEM=0.003) in the CW direction and 0.638 c/d (SEM=0.004) in the CCW direction. When the bilateral lesion was then completed by a lesion to left V1, acuities initially dropped to 0.501 c/d (SEM=0.007) CW and 0.496 c/d (SEM=0.005) CCW, followed by a slight recovery of

function by 4 weeks post-surgery to 0.514 c/d (SEM=0.004) CW and 0.508 c/d (SEM=0.005) CCW. These final acuity values were significantly different from the pre-lesion acuity ($F_{(3,18)}=4049.93$, $p<0.0001$), but not different from naïve animals (chapter 2; figure 6) that received the same lesions ($p=0.0629$).

Bilateral removal of V1 the day before eye-opening had a similar effect to bilateral V1 removal in adulthood. Acuity of lesioned animals that began testing on P15 was significantly different from a normal developmentally enhanced group on every day from P15-P30 ($F_{(1,160)}=1420.722$, $p<0.0001$) and reached an optomotor sensitivity threshold of 0.525 c/d (SEM=0.002) (figure 12A). Lesioned animals tested from P15 did not differ ($p=0.6066$) from lesioned animals that began testing at P25 (0.524 c/d; SEM=0.002). At P25-P30 both groups of lesioned animals were significantly lower than intact animals tested from P15 (0.853 c/d; SEM=0.001) and only slightly lower ($F_{(3,84)}=36102.488$, $p<0.0001$) than an intact group that started testing at P25 (0.541 c/d; SEM=0.001).

Experiential control of optomotor enhancement

Static stimulus exposure

All animals that received the moving stimulus were able to track from P15 and had enhanced thresholds similar to those of other visuomotor enhanced animals reported previously. The average acuity of the enhanced animals was 0.852 c/d (SEM=0.003), while the sensitivity of the animals receiving the static grating stimulation was 0.564 c/d (SEM=0.003) (figure 13). As adults the two groups were significantly different

($t_{(3)}=166.277, p<0.0001$), and the static group was slightly higher than naïve animals tested previously ($t_{(3)}=8.051, p=0.0040$).

High/low spatial frequency exposure

From the day of eye-opening all animals exposed to a low spatial frequency grating (0.031 c/d) actively tracked the stimulus, while animals exposed to a high spatial frequency (0.831 c/d) never tracked the stimulus. Both groups had thresholds higher than animals that were naïve at P25 or adults, however, they were lower than normal enhanced animals ($F_{(3,16)}=5074.019, p<0.0001$). All groups were significantly different from each other. At P30 (figure 13) the low and high spatial frequency exposure groups had thresholds of 0.654 c/d (SEM=0.002) and 0.710 c/d (SEM=0.002), respectively, values that had not changed from P25 ($F_{(5,18)}=1.618, p=0.2058$ and $F_{(5,18)}=0.843, p=0.5369$, respectively).

One direction exposure

The acuity in the direction that animals were exposed to from eye-opening continued to change ($F_{(15,48)}=5368.654, p<0.0001$) until ~P27 and reached a maximum threshold of 0.819 c/d (SEM=0.004) at P30 (figure 13B). When compared to normal enhanced animals, the acuity of rats exposed in one direction were significantly lower on all days from eye-opening to P30 ($F_{(15,128)}=14.725, p<0.0001$), although the difference was not large. Thresholds measured through the eye corresponding to the deprived direction were 0.560 c/d (SEM=0.002) at P25 and increased to 0.576 c/d (SEM=0.002) by P30. At P30 the acuity of the deprived direction was significantly lower than that of

normal animals tested from P15 and acuities in the exposed direction, but was higher than a naïve group ($F_{(3,96)}=25970.407, p<0.0001$).

The effect of optomotor experience on visual perception: Visual Water Task

Training

All rats learned to associate swimming to the platform with escape from the pool. Approximately 100 trials were needed for the animals to reach 90% accuracy over 40 trials on the first task, while subsequent tasks required less training. All animals learned to grasp the end of the divider and inspect both screens before making a choice.

'Static' grating acuity

In the first experiment with the stimulus being grey vs. grating (figure 14A) both groups performed the task with near perfection up to a spatial frequency of ~ 0.8 c/d. Around this point both groups began to make errors, although they remained above the 70% criterion until about 0.95 c/d. The acuity of the group tested from P15 was 0.965 c/d (SEM=0.068), while the acuity of the P25 group was 0.953 c/d (SEM=0.034) (figure 14B). The acuities between the groups did not differ significantly ($t_{(5)}=0.153, p=0.884$) (figure 14B). The values from both groups were similar to what have been reported previously (Dean, 1981a; Prusky *et al.*, 2000a).

'Moving' grating acuity

Due to the previous training in the VWT, animals were quickly able to learn to discriminate between gratings moving in opposite directions (figure 14C). The P15 group performed at near perfection to about 0.65 c/d, while the P25 animals began

making errors around 0.45 c/d. The P15 animals had an acuity of 0.735 c/d (SEM=0.041) while the P25 group acuity was 0.512 c/d (SEM=0.021). Animals tested in OptoMotry from eye-opening were significantly better at detecting moving gratings than animals not tested until P25 ($t_{(5)}=5.646$, $p=0.002$) (figure 14D).

Dot motion coherence threshold

Changing the stimulus from gratings to dots required some training, but all animals were able to learn the task. Both groups were able to perform the task at near perfection until about 40% coherence. At this point the animals began to make errors, but remained above criterion until approximately 25% coherence. Coherence thresholds of animals tested in OptoMotry from eye-opening was 24.5% (SEM=1.45), while the threshold for the P25 group was 23.7% (SEM=0.955). There was no significant difference between the two groups ($t_{(5)}=0.605$, $p=0.571$) (figure 15B).

Dot motion size threshold

This task was learned easily because of its similarity to the previous dot coherence experiment. Animals tested in OptoMotry from eye-opening performed to near perfection to dot sizes of $\sim 0.1^{\circ}$, but the performance of the P25 animals began falling off at 0.4° . The enhanced group was able to discriminate the two stimuli down to a dot size of 0.075° (SEM=0.011), while the P25 group had a threshold dot size of 0.353° (SEM=0.015). Animals tested from eye-opening were able to detect a significantly smaller dot size than animals not tested until P25 ($t_{(5)}=15.03$, $p=0.00002$) (figure 15D).

Summary

Characterization of a visuomotor critical period

The results show that a form of experience-dependent plasticity, distinct from the critical period, exists and allows for the enhancement of motion vision. During the course of characterizing the optomotor response in the previous chapter it became evident that animals tested from eye-opening in OptoMotry had higher optomotor acuities than experimentally naïve animals measured for the first time as adults. A within-litter experiment in this chapter confirmed that animals tested from P15 reach higher thresholds than animals that begin testing at P25; in fact we saw a 38% higher optomotor acuity in the experienced animals. This is the first significant evidence for an enhancement of function by visual experience. Also, these studies provide some of the first behavioural measures of vision in developing rats. Using a virtual optomotor task one can measure effectively the visuomotor sensitivity of rats from the day of eye-opening and detect developmental changes during that time. This has long been a limitation of behavioural vision tasks and even electrophysiological tasks often require the use of different animals on subsequent days of testing due to their invasive nature. These previous tasks would not allow for the identification of an enhancement effect caused by numerous sessions of visual experience such as those done here.

In regards to contrast sensitivity, there was no effect of the early testing at the spatial frequencies measured up to and including the peak of the curve (0.1 c/d), however, at the higher spatial frequencies animals tested from P25 had better contrast sensitivity. Though the curves differed slightly, both had the characteristic inverted “U”-shaped function that has been shown previously by others (Keller *et al.*, 2000; McGill *et*

al., 2004a). In measuring the two groups, we often observed a behaviour termed “anti-tracking” in animals tested from eye-opening, but not in littermates tested from P25. When gratings were placed on the monitors, the animals would briefly track it and then switch directions so that they were moving their head in the opposite direction of the gratings. This behaviour occurred intermittently while measuring acuity, but became much more frequent while measuring contrast sensitivity at spatial frequencies higher than the peak of the curve. This behaviour began at ~P20 and continued into adulthood. The points at which anti-tracking most occurred corresponded to the points of the contrast sensitivity function where the animals tested from P25 had higher values; that is, the anti-tracking may account for the difference in contrast sensitivity that was observed. The cause of the behaviour is unknown, but will be investigated in the future. Due to the small effect of the early testing on contrast sensitivity, optomotor sensitivity will be focused on for the remainder of this thesis.

Upon further inspection of the “critical” period for the enhancement of optomotor sensitivity, it was found to have the same characteristics as that of other critical periods. That is, there is a transient period of plasticity that allows for an alteration in function depending on the visual environment (e.g. Hubel *et al.*, 1977, Blakemore & Van Sluyters, 1974). The majority of the plasticity occurred before the peak at P19. These temporal properties suggest that the period of optomotor plasticity is distinct from the critical period for MD, which does not start until P21 and has a peak in plasticity at ~P30 (Guire *et al.*, 1999), and provides evidence to support the existence of a critical period for motion vision (Daw & Wyatt, 1976) being distinct from that of the critical period for form vision. Though these results are similar, they have one major difference in that

there is an enhancement of motion vision, rather than a loss of visual function. This difference is likely due to the difference between the nature of the visual behaviour that was tested here compared to the visual functions that have been measured in previous deprivation experiments. Regardless of that fact, only deprivation effects have been induced during the critical period of OD plasticity and such a distinct critical period for any visual function has not been identified until now.

Role of the cortex

It has been previously shown that OKN (Harvey *et al.*, 1997) and head tracking (chapter 2; Douglas *et al.*, 2005) in rats is not effected by cortical lesions. However, removal of V1 in animals with visuomotor experience from eye-opening or before eye-opening results in a loss of visual acuity from enhanced levels or a lack of enhancement, respectively. The effects these lesions have on enhanced animals are similar to those shown for cats and monkeys, where a loss in OKN is caused by cortical lesions (Flandrin *et al.*, 1992; Segraves *et al.*, 1987). This similarity in effects suggests that the enhanced acuity in developmentally exposed rats may be caused by a conferral of cortical control over the visuomotor system, as it is in cats and monkeys for OKN. As was described in the previous chapter, there is a cortical projection to the AOS, but it is thought to have no effect on the thresholds produced by the subcortical circuitry. The lesion experiments done here provide significant evidence that early testing may involve this cortical projection, thus sending information concerning motion to the subcortical nuclei involved in the optomotor response. The cortico-subcortical projection to the AOS seems to convey high spatial frequency information to the subcortical circuitry, while efferents

from the retina convey only low spatial frequency information. Without early exposure only low spatial frequency information from the retina reaches the subcortical structures, therefore, naïve adult animals have lower optomotor thresholds, such as those reported in chapter 2.

The partial recovery in function following sequential unilateral lesions of animals tested from P15 is similar to previous results (Strong *et al.*, 1984) in cats and provides more evidence to support the similarity between head tracking in optomotor enhanced rats and OKN in cats and monkeys. The similarity in results also indicates that the enhancement in function is due to an alteration in the visual cortex. Cats given unilateral visual cortex lesions have deficits in both directions of OKN, particularly toward the side of the lesion. This loss is much like the one reported in this current work with rats where there was an initial drop of optomotor sensitivity in both directions, particularly in the direction that corresponded to the side of the lesion (i.e., a left V1 lesion leads to a lower sensitivity in the CCW direction and right V1 lesions cause a reduction in the CW direction). Moreover, following a unilateral V1 lesion in cats, there is a recovery of OKN in both directions in a sort of ‘balancing’ that reduces the asymmetry (Strong *et al.*, 1984). This balancing was also shown in our results and suggests that a single hemisphere can partially mediate the optomotor response in both directions when animals are exposed to motion stimuli from eye-opening.

Experiential control

In previous experiments involving motion, the effects have been induced by deprivation (Cynader *et al.*, 1975; Daw & Wyatt, 1976). However, stimulus control was

generally limited to the direction of rotation, the speed of rotation and only one spatial frequency was used during the exposure period. Also, the behavioural visual thresholds that resulted from this exposure were not measured. Using the optomotor system developed here, the stimulus can now be controlled to a greater extent, in particular the spatial frequency.

OKN drums have been more effective at testing the motor aspect of optomotor responses (Collewijn, 1977; Marlinsky & Kroller, 2000), however, due to the high degree of stimulus control, OptoMotry can be used to quantify both the motor and sensory (Douglas *et al.*, 2005) portion of the behaviour. The thresholds obtained from animals exposed to a low spatial frequency that they always actively tracked from P15-P25, indicate that the motor aspect of the behaviour is necessary, but not sufficient to create a maximal enhancement in acuity. Conversely, exposure to a high spatial frequency that the animals had never actively tracked, resulted in higher thresholds, but again the maximal effect was not obtained. Though no tracking of the high spatial frequency stimulus occurred, the animals were probably still able to perceive the stimulus without producing any motor output. This perception could have happened at the level of the cortex where higher spatial frequency information is processed and then passed on to the subcortical structures through the cortical-subcortical projection, as suggested above. Thus, giving the sensory system visual experience is also important to produce the maximal enhancement of acuity. These results again suggests that the cortex is involved in the optomotor enhancement because the rats most likely began perceiving the high spatial frequency stimuli part way through development due to cortical maturation and the cortex's ability to discriminate high spatial frequency information. With that said,

obtaining threshold values of ~ 0.85 requires animals experience high spatial frequency, moving stimuli that generates optomotor head tracking.

In an alteration to the direction deprivation experiments done by Daw and colleagues (1976), exposure to gratings moving in one direction from P15-P25 does not result in a deprivation effect when measured at the level of behaviour. Though our animals were only deprived of one direction of movement for the duration of the testing session, rather than all of development, exposure in the other direction was enough to induce a large enhancement in optomotor sensitivity. Upon measuring thresholds at P25, the acuity measured through the eye corresponding to temporal-to-nasal drum rotation was enhanced to near its maximum, while acuity through the other eye was enhanced only slightly above that of naïve animals. These results give further validity for the application of this system to do within-animal controls. The fact that maximal acuity was not reached in one direction and was higher than that of naïve animals in the other, suggests that the visual input from the retina to the cortex is not completely crossed. It is possible that the small ipsilateral projection from each eye to the visual cortex (Grieve, 2005) accounts for the sub-maximal thresholds. For example, when exposing animals in the CW direction, acuity through the left eye is being tested, and in this case enhanced. That means that the right visual cortex is undergoing some change to cause the enhancement, however, some of the projections from the left eye are going to the left visual cortex. Also, because the optomotor response is not being driven by the right eye, no enhancement of function is occurring in the left visual cortex, but left V1 is receiving some projections from the ipsilateral eye. This partial crossing suggests that exposure

must occur in both directions of rotation and that the ipsilateral projection is necessary for maximal acuity to be reached.

Enhanced motion perception

Due to the existence of a cortical projection to the subcortical nuclei and because lesions cause a loss of enhancement, it is plausible that cortical changes due to early optomotor experience, may also have led to enhanced visual perception, a cortically mediated ability. As might be expected, there was no enhancement in the ability to detect static gratings. However, when the task was altered to become a moving grating discrimination task, the animals tested from eye-opening in OptoMotry were able to discriminate a higher spatial frequency moving stimulus than their littermates. This increase in moving grating perception provided the first evidence that the optomotor enhancement originally described was in fact an enhancement in the ability to detect motion as a whole, independent of whether it is of subcortical or cortical origins.

With the previous finding in mind, motion detection was also assessed in a dot motion coherence task. It has become common to use dynamically moving random dot patterns (or kinematograms) to assess visual motion, as they enable the study of motion perception in the absence of positional or form cues (Nakayama & Tyler, 1981).

Perceptual mechanisms that can detect common motion of many elements have been identified in humans and other primates (Braddick, 1974; Morgan & Ward, 1980; Williams & Sekular, 1984) and localized to extrastriate cortex (Newsome & Paré, 1988; Baker *et al.*, 1991). In order to complete the task, animals must rely on the motion of all the dots (global motion) rather than just single dots that may be moving randomly. Here,

we found no difference in the ability of animals to detect global motion (dot motion coherence). From this it can be inferred that the enhancement in perception must be specific to the stimulus, most likely of a high spatial frequency nature. When the dot size was then reduced, the animals with early optomotor experience were able to detect a smaller dot size down to something resembling static on a TV screen. Thus, the ability to respond to high spatial frequency moving information was enhanced in a perception task much like it was in the optomotor task.

The identification of a critical period for motion vision is important to the understanding of the visual system. Within the classic critical period multiple periods of plasticity have already been identified with small differences in the timing and effects that the visual environment can have during those times. The plasticity for motion vision described here is another one of these periods; however, it was quantified through an enabling effect, in contrast to the deprivation effects that characterize all of the other plastic periods. It also appears to occur much earlier than any other period previously described. The enhancement of both visuomotor function and motion perception provides evidence that the cortex is conveying information to the subcortical structures, most likely concerning high spatial frequency information. If this plasticity was limited to the nuclei of the AOS, then removal of the cortex would have had no effect. Moreover, the perception of motion stimuli would not be enhanced if the changes that took place were not associated with visual cortex. This makes this critical period for motion vision a distinct critical period from those previously described in deprivation studies.

Chapter 4-Discussion

The experiments presented in the preceding chapters have shown that a novel task for testing optomotor responses, known as OptoMotry, is effective at measuring visuomotor thresholds in rats daily from eye-opening. During the course of this work, a critical period for the development of visuomotor sensitivity was characterized which precedes the classic critical period for the negative effects of visual deprivation on visual cortex function. This period of enhancement required that animals experience high spatial frequency moving stimuli that generate optomotor head tracking, and was also shown to be dependent on visual cortex. The enhancement in visuomotor function was also accompanied by an enhancement in the sensitivity of visual motion perception, as demonstrated in experiments utilizing the Visual Water Task. The ability of transient visual experience from eye-opening to permanently enhance visual function is novel, and indicates that a previously undetected form of visual system plasticity is present from eye-opening, well before the classic critical period.

4.1 Enabling of visual function through experience

Virtually all previous research reporting developmental plasticity in the visual system has used visual deprivation as the experimental variable (i.e. MD, induced blur or strabismus, one orientation and one direction rearing). The loss of function as the result of visual deprivation during the classic critical period, has generally been interpreted as meaning that the missing visual experience normally *enables* function. Since visual deprivation before the critical period does not result in an OD shift or a loss of visual

acuity, most researchers have concluded that there is not significant enabling plasticity outside of the critical period. The experiments in this thesis, show that the period of time from eye-opening to the onset of the classic critical period is in fact a period of significant visual plasticity. The plasticity, however, is in the visual motion system, rather than the form vision system, and is characterized by an enhancement, rather than a loss of function. Visuomotor testing during this new critical period could have at least two effects on the motion vision system. First, it may allow an animal to overcome the effects of existing deprivation; that is, normal cage reared animals may be deprived of visual experience and testing replaces the missing experience. Alternatively, visuomotor experience may provide a ‘super-normal’ experience that results in higher thresholds than would be observed under other circumstances. The enhancement would then be considered an experience-dependent *enabling* of function. These possibilities will be discussed in the following sections.

4.1.1 Overcoming visual deprivation?

Rats reared in standard laboratory housing spend nearly all of their lives in relatively small cages. These conditions are not normal and rats in the wild are likely to be exposed to more moving visual stimuli during development, both self induced and environmentally derived. Therefore, the enhancement of motion vision as a result of visuomotor testing from eye-opening, may be the result of replacing visual motion experience that it is being deprived under our laboratories cage rearing conditions. To test this hypothesis, more naturalistic forms of visual stimulation could be administered from eye-opening to P25 and the effect of that experience measured. Examples of this may

include enriched rearing through complex housing, and/or open field experiences where animals are placed on a table in a room with a variety of moving visual cues and where animals can move more freely than in a cage.

Numerous studies have shown that rearing animals in an enriched environment can lead to changes in dendritic arborization, spine density and synapses per neuron (in the cortex, hippocampus and cerebellum) (Rosenzweig, 1966; Greenough and Volkmar, 1973; Renner and Rosenzweig, 1987; Rampon *et al.*, 2000; Kolb, 1995). These morphological changes are associated with improved learning and memory, enhanced neural plasticity (reviewed in van Praag *et al.*, 2000) and reorganization of cortical somatosensory maps (Polley *et al.*, 2004). Fewer studies have found an effect of enriched housing on the visual system; although, enrichment has been shown to increase dendritic branching in visual cortex (Kolb & Gibb, 1991) and postweaning environmental enrichment prevents the adverse effects of dark rearing on rats (Bartoletti *et al.*, 2004), while enrichment from birth in mice causes conspicuous acceleration of visual system development at behavioural (Prusky *et al.*, 2000), electrophysiological, and cellular levels (Cancedda *et al.*, 2004). It is possible that the enhancement reported in these experiments is related to the transient enhancement of motion vision described in this thesis.

However, because animals were enriched from birth through to young adulthood, the above enrichment studies did not restrict the novel experience to the period between eye-opening and P25; therefore, the specific time during which the enhancement occurred is unknown. Furthermore, static visual acuity was measured, not visuomotor or perceptual visual motion thresholds; the measures of vision that were enhanced in my experiments. The enhancement described in this thesis is restricted to the period from eye-opening to

P25 and results only in an enhancement of motion vision (static acuity in animals tested from eye-opening was not different than experimentally naïve animals). Preliminary results from our lab, however, show that neither enrichment by continuous complex housing or daily open field experience, from P15-P25, result in an enhancement of visual motion function (Prusky & Secretan, in preparation). This suggests that the enhancement of motion vision driven by optomotor testing from P15-P25 is not simply overcoming an inherent deprivation of visual motion experience in cage rearing conditions.

4.1.2 Enabling visual function?

A second possibility is that the enhancement in visuomotor sensitivity is a true *enabling* of function. This enabling may be in response to a “super-normal” experience. That is, the stimulation provided through optomotor testing may not be “normal”, but rather abnormal experience that takes advantage of visuomotor plasticity that is present only after eye-opening. Supporting evidence for this hypothesis is present in the experiments reported in this thesis. First, not testing the animal or not moving the cylinder in optomotor task from P15-P25 results in the same visuomotor sensitivity (0.53 c/d). In addition, testing the animals in only one direction in the testing arena provided moving stimuli, but only enhanced the animals’ vision in one direction (figure 13). In other words, the eye corresponding to the non-tested direction experienced moving stimuli of all moving spatial frequencies and contrast, but still its vision was not dramatically enhanced. These data, together with those showing the stimulus specificity of the enhancement, indicate that the enhancement of visuomotor sensitivity from P15-P25 is the result of driving specific optomotor circuitry. This interpretation is confirmed

by preliminary experiments from our lab showing that BD from P15-P25 results in normal (0.530 c/d) visuomotor sensitivity (Prusky & Tschetter, in preparation). If removing normal experience with BD does not result in a loss of function, it makes the enhancement of function observed with testing with both eyes open from P15-P25 stand out clearly as a dramatic enhancement. The plasticity observed in the above experiments also stands in stark contrast to that identified during the classic critical period. The observation of plasticity during the critical period is based exclusively on the negative effects of deprivation, whereas, in the present experiments deprivation (or null testing) result in no negative effects; the plasticity is the result of an enhancement of function.

If enabling plasticity is present in the visual system at eye-opening, it is likely that that plasticity depends on the visual cortex (figure 11). The specific role of this cortically mediated function is not clear at this time. Clearly, cage reared animals have functional optomotor responses, but those responses are tuned to low spatial frequencies (i.e., those below 0.53 c/d). This low spatial frequency tuning characteristic of subcortical optomotor circuitry (Grasse & Cynader, 1984; Soodak & Simpson, 1988; Schmidt *et al.*, 1993), is ideal for stabilizing the retinal image of the animals' general environment an animal is in and is purely reflexive. In addition, that removal of visual cortex before testing is initiated at P15 results in no enhancement, indicates that this subcortical circuitry has little experience-dependent plasticity. That the higher spatial frequency optomotor responses observed following visuomotor testing from P15-P25 require an intact visual cortex suggests that the plasticity in visuomotor function resides within the cortex. This cortex mediated plasticity for visual motion may account for the enhancement in visuomotor sensitivity, and may have at least two functions. First, the

enhancement may be an extension of the subcortical responses that animals already have; that is, high spatial frequency input to the subcortical nuclei results in the same reflexive stabilizing response, but now this also occurs in response to high spatial frequency information. However, these reflexive responses to high spatial frequency information may cause the animal to be somewhat hypersensitive; that is, an animal would respond to much more information than is necessary to stabilize the visual scene, which would likely be detrimental to their survival. The second possibility is that the enhanced response is not reflexive, but rather voluntary. Voluntary control would mean that an animal can control its responses to high spatial frequency moving information. Therefore, anything above normal thresholds of cage reared animals (~ 0.53 c/d) would be a voluntary response. We could not distinguish between voluntary and involuntary responses in these studies, but future experiments will address this.

4.2 Mechanisms of plasticity

The cellular mechanisms by which plasticity in the critical period for motion vision occurs in general, is unknown. It is clear that the visual cortex is involved in some way, but the actual cellular changes that take place were not the focus of experiments detailed here. Though plasticity during the classic critical period is not completely understood, many of the necessary cellular and molecular changes are known and may share some commonality with the mechanisms involved in the critical period of motion plasticity.

4.2.1 Possible molecular mechanisms

Several molecules and receptors have been identified as being involved in the changes that take place during the classic critical period of heightened cellular plasticity. For example, blocking the N-methyl-D-aspartate (NMDA) receptor or altering its subunit makeup is known to prevent plasticity from occurring (Bear *et al.*, 1990; Carmignoto & Vicini, 1992; Flint *et al.*, 1997; Roberts *et al.*, 1998; Roberts & Ramoa, 1999). Also, the increased expression of neurotrophins, in particular brain-derived neurotrophic factor (BDNF), have been shown to accelerate both the development of visual acuity and the time course of ocular dominance and synaptic plasticity (Berardi *et al.*, 1994; Cabelli *et al.*, 1997; Huang *et al.*, 1999). In addition, gamma aminobutyric acid (GABA) inhibition is thought to be important in determining the onset of the critical period; antagonists or mutations of the GABA receptor result in a loss of plasticity (Fagiolini & Hensch, 2000). That the plasticity described in this thesis is experience-dependent, suggests that the mechanism of plasticity for visual motion may be similar to those of the classic critical period discussed above. However, cellular changes during the classic critical period are caused by deprivation rather than increased experience, and result in a loss of function rather than an enhancement of function, and occur later in development than the critical period for visual motion described in this work. The behavioural consequences and temporal differences in the plasticity between the classic critical period and the visual motion critical period, combined with a lack of research identifying the mechanism of visual motion plasticity, makes it impossible to conclusively determine the neural substrates of the changes observed here, and will require future research.

4.2.2 Proposed models of enhancement

Though the cellular changes that take place during the enhancement of visuomotor sensitivity are not known, models of this enhancement can be proposed (figure 17). Experiments in this thesis have shown that an intact cortex is necessary for both the development and maintenance of the enhancement, indicating that the cortex is involved in the responses generated. However, it is not clear where the changes occur that lead to this enhancement in visuomotor function. There are two probable locations for these changes: either the synapses of cortical connection onto the subcortical structures are strengthened and activated, or the plasticity occurs in the visual cortex, which has downstream effects on the subcortical circuitry. It is also possible that both occur. Both hypotheses are discussed below.

As was previously described, there is anatomical and physiological evidence in rats for cortical projections to the AOS (Takada *et al.*, 1987; Giolli *et al.*, 1988; Schmidt *et al.*, 1993), but the exact function of this connection is unknown. It has been proposed that the cortical pathway is primarily there to cope with translational movements that change the distance to an attended optic flow field (Miles, 1998). However, because the enhancement of visuomotor sensitivity depends on cortex and this cortico-subcortical connection is the only one, then the function of the cortical projection may be to convey information to the AOS pertaining to high spatial frequencies. This transfer of high spatial frequency information is possible because the receptive fields of cortical cells are smaller than those of the subcortical nuclei, allowing for higher resolving power in the cortex (Schmidt *et al.*, 1993). Though cortical input was not confirmed in my experiments, presumably it is present in all the rats tested. Therefore, one possible site

for the cellular changes that occur during the motion vision plasticity may be at the synapses between the cortical projection and the nuclei of the AOS. That is, the increase in visuomotor experience may result in a strengthening of the synapses. This alteration in synapses may allow for the normal resolving power of the cortex to influence the subcortical nuclei that generate the optomotor response. However, experiments using the VWT showed that the perception of motion is also enhanced in animals with optomotor experience from eye-opening. That the VWT is sensitive to alterations of cortical function, such as lesions and ocular dominance shifts as a result of MD (Prusky *et al.*, 2000c; Prusky & Douglas, 2003; Prusky & Douglas, 2004a), suggests that the enhancement in motion vision occurs at the level of the cortex. If visual cortex was unchanged in animals tested from eye-opening, then they would likely show no enhancement in motion perception, there would be no difference in the receptive field size of cells in visual cortex between enhanced and naive animals, and thus, they would have equal motion grating acuity (see figure 14).

The second possible location of plasticity for visual motion is the cortex. As described above, there is an enhancement in motion perception due to early optomotor experience that may result from alterations in cortical function. In addition, cells in primary visual cortex in rats have been shown to have very good motion and directional tuning (Girman *et al.*, 1999), allowing for processing of high spatial frequency moving information. This high spatial frequency information may be projected through the cortical input onto the NOT and DTN of the AOS. The cortical projection is known to originate from V1 and extrastriate area V2 (Schmidt *et al.*, 1993), which coupled with the evidence described above, supports the hypothesis that the cortex is the major site of

visual motion plasticity. This plasticity likely results in even better motion and direction tuning of cells in the cortex, and may also cause responses to higher spatial frequency moving stimuli than normal cage reared animals would demonstrate. The cellular changes that may occur in the cortex likely do so in different circuitry and at a different time than the ocular dominance alterations due to deprivation during the classic critical period because static acuity was not affected by visuomotor experience. That lesions of V1 abolished the visuomotor enhancement in animals that experienced moving stimuli, suggests that the high spatial frequency processing done by V1 must move downstream directly to the subcortical circuitry or other cortical centers. Extrastriate area V2 may be a site of plasticity because that is where part of the cortico-subcortical projection originates. The anterolateral (AL) visual area is also a possible substrate because it has been shown to respond to visual motion (Montero & Jian, 1995).

4.3 Final comments

In summary, the results of these studies provide the first substantial evidence for an experience-dependent enabling of visual function during development. This enabling effect is due to increased optomotor experience from eye-opening to P25 and is likely caused by changes in cortical function. These changes characterize a novel critical period for visual motion that precedes the classic critical period for deprivation effects. Characterization of this novel critical period will provide researchers with another instance of plasticity to explore, and one that is easily inducible in a short time. It is important that the anatomical, physiological and behavioural consequences of this

plasticity be quantified. In a system thought to be well understood, relative to the rest of the brain, this finding shows that there is much that is yet to be discovered.

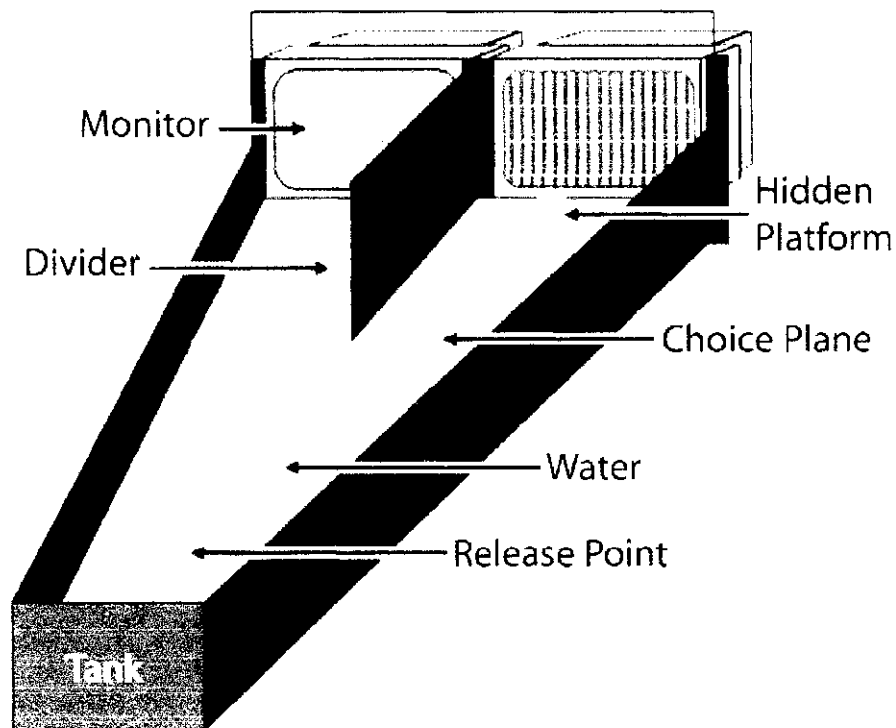


Figure 1. The Visual Water Task. Apparatus consists of a trapezoidal-shaped tank with a midline divider at the wide end, creating a maze with a stem and two arms. Computer monitors located outside of the maze project into each arm through a clear wall. A reinforced (+) stimulus (i.e. sine wave grating) is displayed on one monitor, and a non-reinforced stimulus (-; i.e. grey) is displayed on the other. The tank is filled with water to a shallow depth and a platform is hidden under the surface of the water, directly below the + stimulus. Animals are trained to swim from the narrow end of the pool toward the monitors. If they choose the arm displaying the + stimulus, they can escape from the water rapidly; if they choose the arm displaying the - stimulus they are forced to swim longer. An imaginary plane defined by the end of the divider, determines whether responses are correct or incorrect. Animals learn to swim to the end of the divider and view each stimulus separately, before making a choice. See text for details.

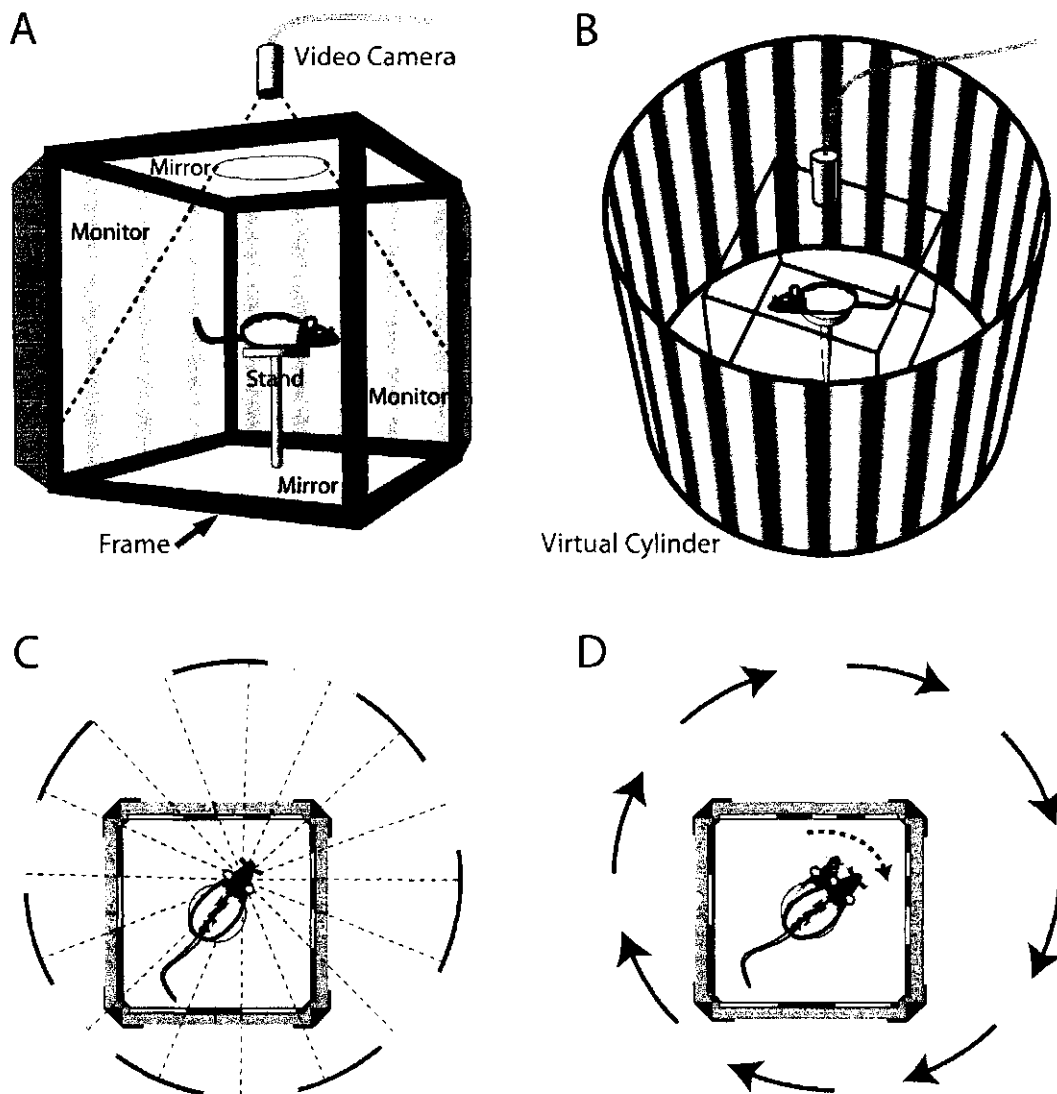


Figure 2. Virtual optomotor system (OptoMotry). **A.** 3D cutaway of the apparatus viewed from the side. A testing arena is framed by four computer monitors; one on each wall, with mirrors on the floor and ceiling. An untrained rat is placed on a platform in the middle of the arena. A video camera images the arena from above. **B.** Virtual view of the apparatus and visual stimulus from above. A virtual cylinder painted with a sine wave grating is drawn on monitors and is projected to surround the animal. **C.** Spatial frequency control. The head of the animal is tracked in real time, enabling the cylinder to be centered at the viewing position, thereby ‘clamping’ the spatial frequency of the grating. **D.** When the cylinder is rotated, rats track (dotted arrow) the gratings with reflexive head and neck movements. Adapted from SFN poster, Douglas *et al.*, 2004 and Douglas *et al.*, 2005.

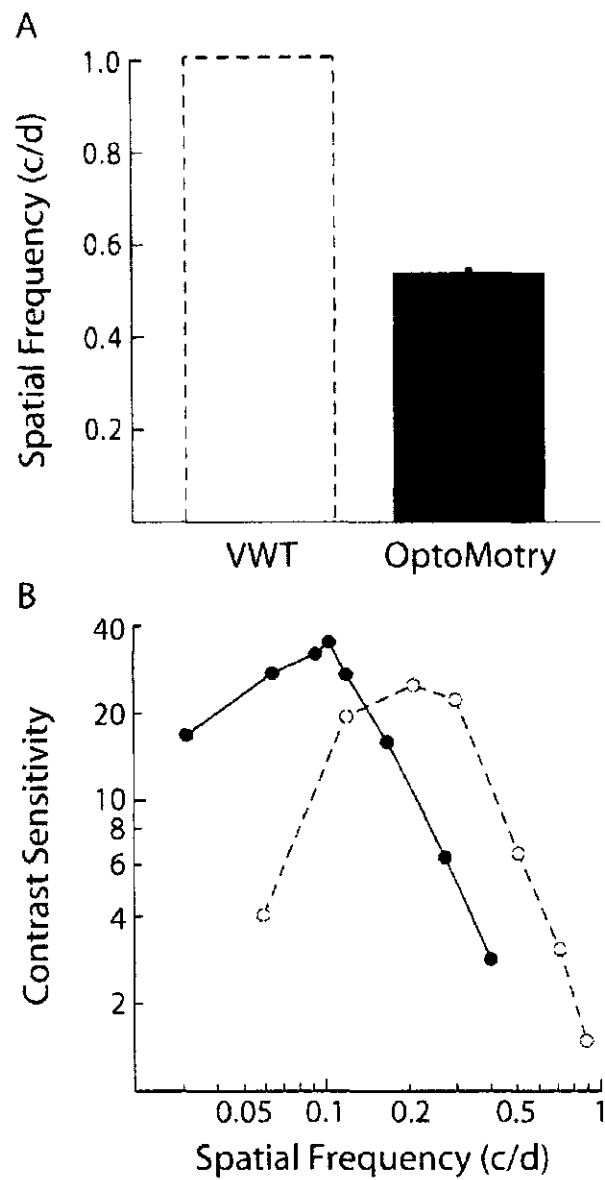


Figure 3. Visual thresholds obtained in the Visual Water Task and OptoMotry differ. **A.** Acuity measured in the Visual Water Task (dashed bar; Prusky *et al.*, 2000a) is higher than that obtained in OptoMotry (solid bar). **B.** Peak contrast sensitivity measured with the Visual Water Task (dashed line; McGill *et al.*, 2004a) is lower than that obtained with OptoMotry (solid line) and the curve is shifted to higher spatial frequencies. SEM is plotted as a vertical line on the OptoMotry bar (A) and is smaller than the symbols on the contrast sensitivity plot (B). See text for details.

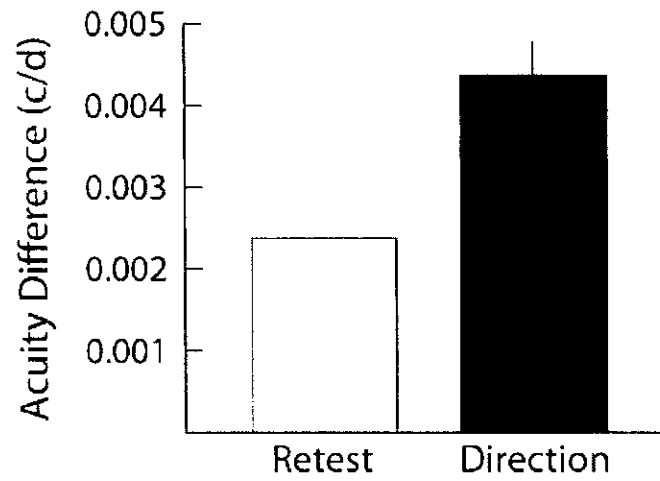


Figure 4. Differences in optomotor thresholds obtained for each direction of drum rotation. The average variation in the measurement of acuity from day-to-day (Retest) was small. Acuity measurements of both directions (Direction) of drum rotation on any given day revealed an asymmetry in thresholds. That is, an animal would consistently have a higher threshold in one direction. Because the variation from day-to-day (Retest) is smaller than the direction asymmetry (Direction), this difference is not likely due to measurement error. SEM is plotted as a vertical line on the bar. See text for details.

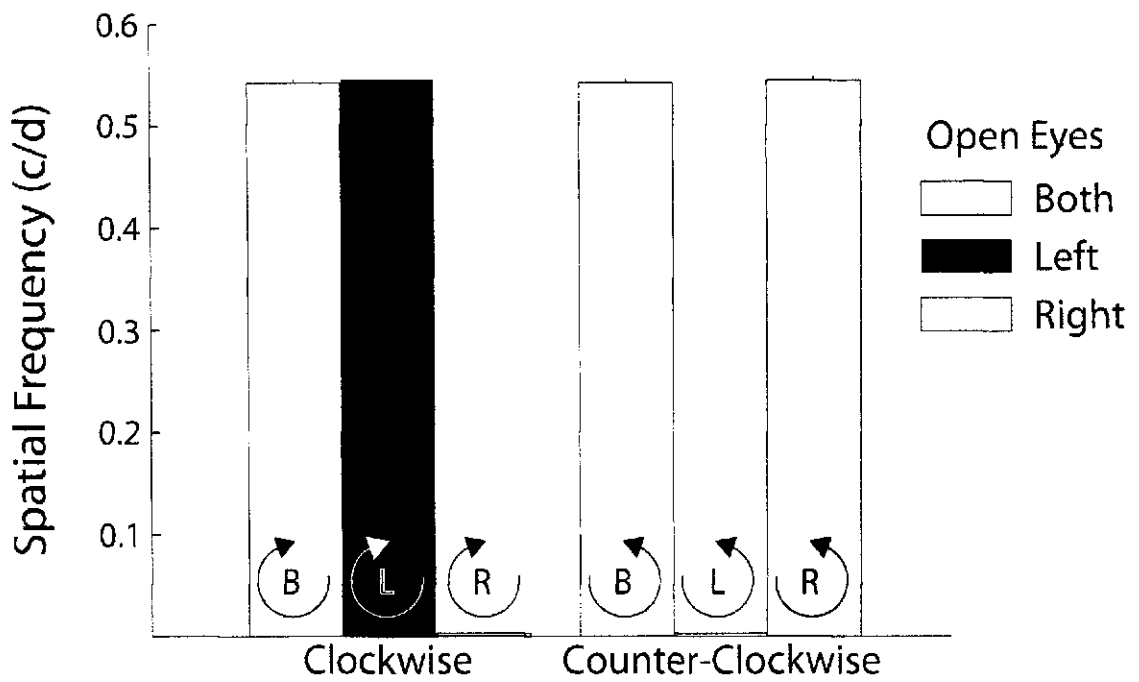


Figure 5. Measurable thresholds depend on the direction of rotation of the virtual drum, and eye. When both eyes are open (white bars) animals track in both directions (Clockwise & Counter-Clockwise). When the right eye is temporarily sutured closed, tracking occurs only in the clockwise direction (black bar). When the left eye is temporarily sutured closed, tracking occurs only in the counter-clockwise direction (grey bar). Thus, tracking occurs only in response to drum rotation in the temporal-to-nasal direction relative to the eye. Visual thresholds through each eye can then be measured independently simply by controlling the rotation direction. SEM is plotted as vertical lines on each bar. See text for details.

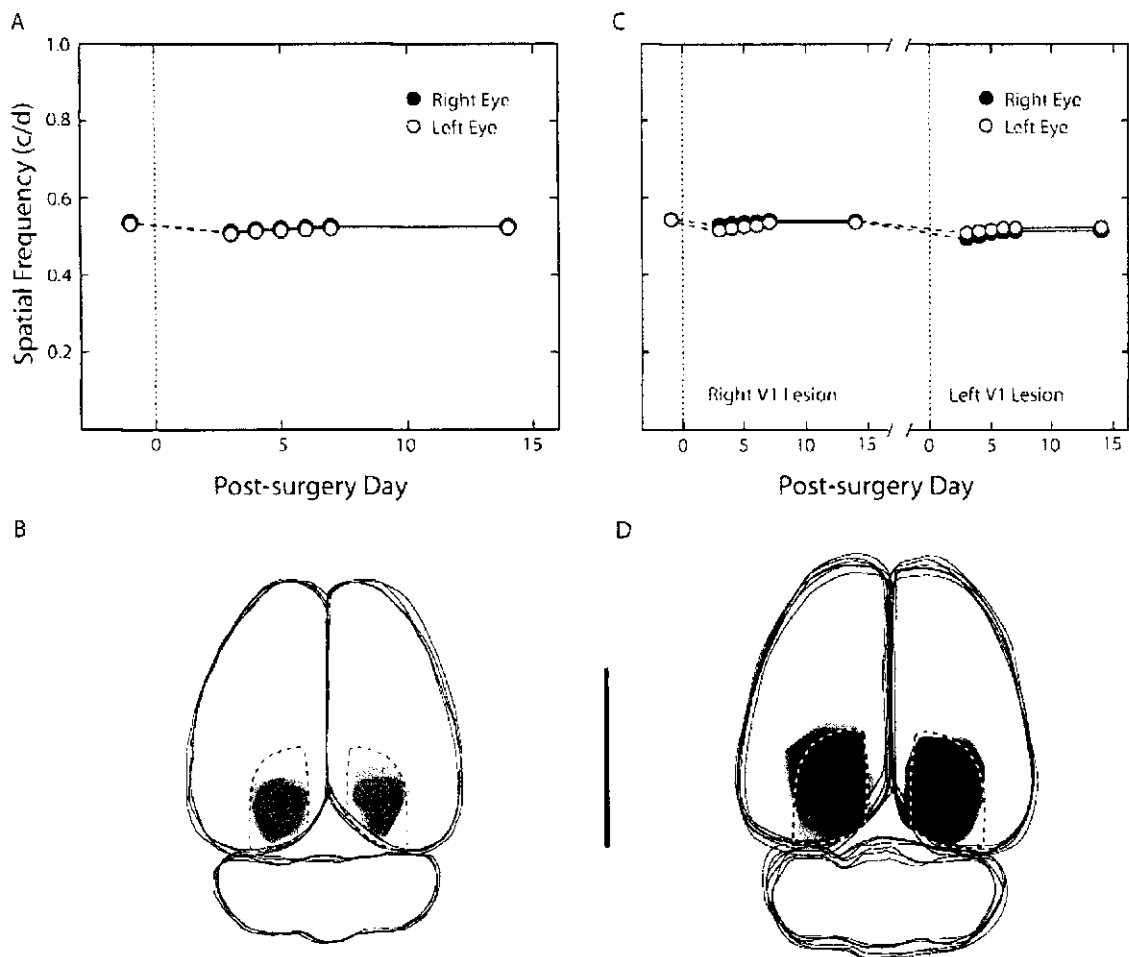


Figure 6. Optomotor responses in experimentally naïve rats depend on subcortical circuitry. **A.** Bilateral primary visual cortex lesions had little effect on the acuity of either eye. Dotted line represents the day of surgery. **B.** Traces of brains from animals in **A** superimposed on one another revealed that lesions were large and that little primary visual cortex remained intact. Dashed line represents the boundaries of primary visual cortex (Paxinos and Watson, 1998). Vertical calibration bar is 1 cm. **C.** Bilateral primary visual cortex lesions done in a sequential manner on experimentally naïve animals had little effect on the acuity of either eye. **D.** Traces of brains from animals in **C** showed that visual cortex lesions were virtually complete. SEM bars are plotted for both scatter plots, but are smaller than the symbols. See text for details.

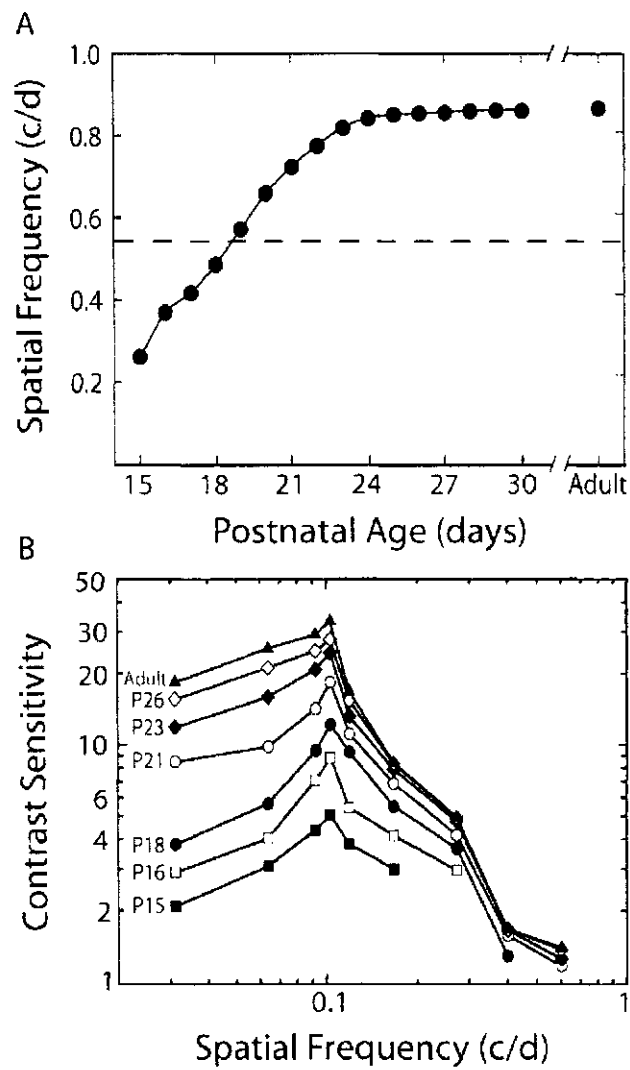


Figure 7. Development of optomotor sensitivity from P15 in Long-Evans rats. **A.** Acuity increased from P15 until P25 where it reached a plateau and remained unchanged thereafter. As adults (~80 days) the acuity of animals tested from P15 was higher than that of experimentally naïve animals tested for the first time in adulthood (dashed line represents acuity from figure 3A). **B.** Contrast sensitivity increased at all spatial frequencies after P15. SEM is plotted, but is smaller than the symbols. See text for details.

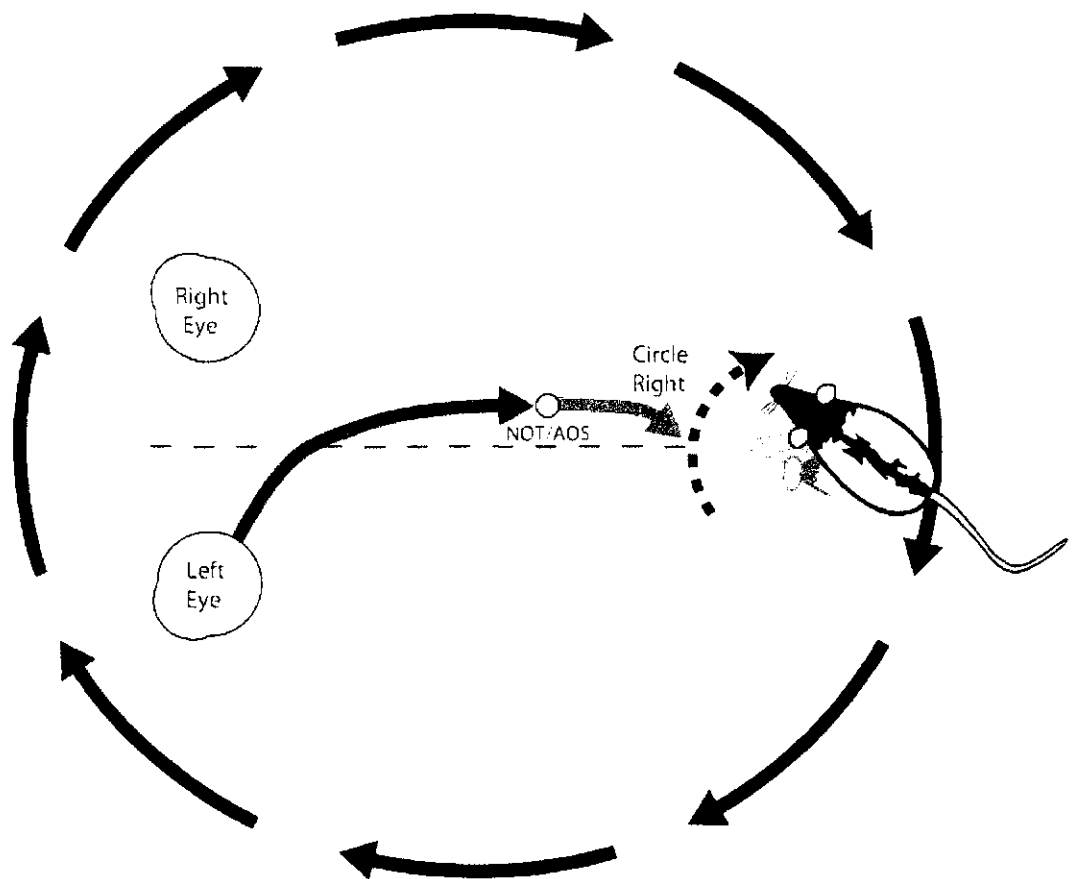


Figure 8. Model of optomotor response in experimentally naïve adult rats. Visual thresholds reflect the properties of the retinal efferents (red arrows) to subcortical structures (open circle), such as the nucleus of the optic tract (NOT) and the accessory optic system (AOS). Although visual cortex receives a large input from the contralateral eye (large blue arrow) and a small input from the ipsilateral eye (small blue arrow), efferents from the cortex to subcortical structures (green arrows) do not contribute to the visuomotor response. Adapted from SFN poster, Douglas *et al.*, 2004.

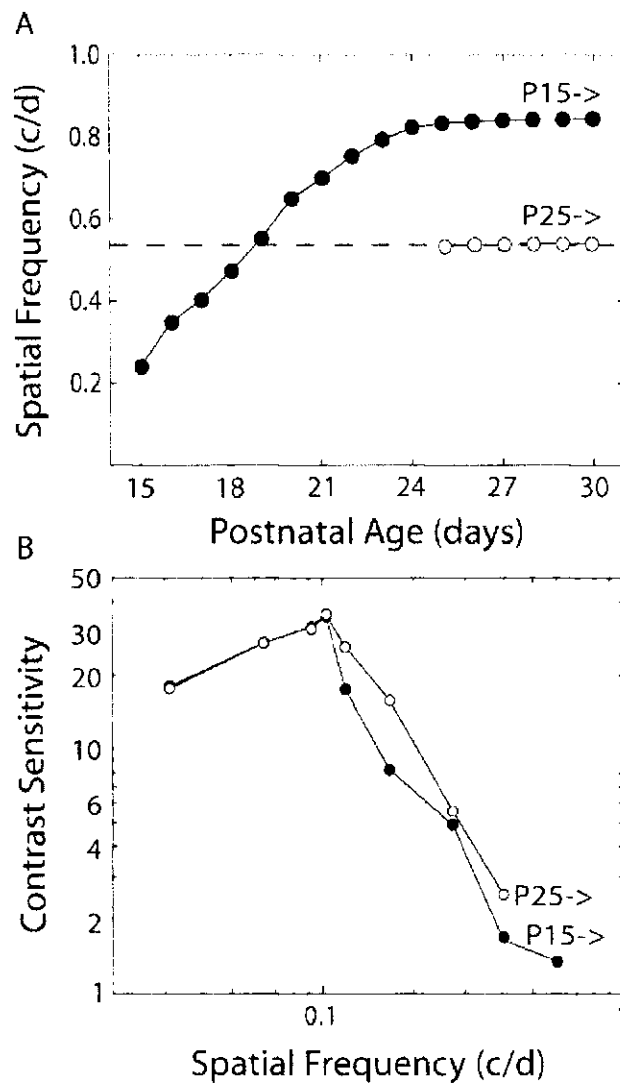


Figure 9. Experience-dependent enhancement of acuity from P15-P25 measured in a “within-litter” design. **A.** Measuring optomotor sensitivity daily from P15 (P15->) enhanced acuity significantly over littermates that began testing at P25 (P25->). P25-> animals did not differ from experimentally naive adults (dotted line; value from figure 3A). **B.** Testing from eye-opening had only a small effect of contrast sensitivity. SEM is plotted, but is smaller than the symbols. See text for details.

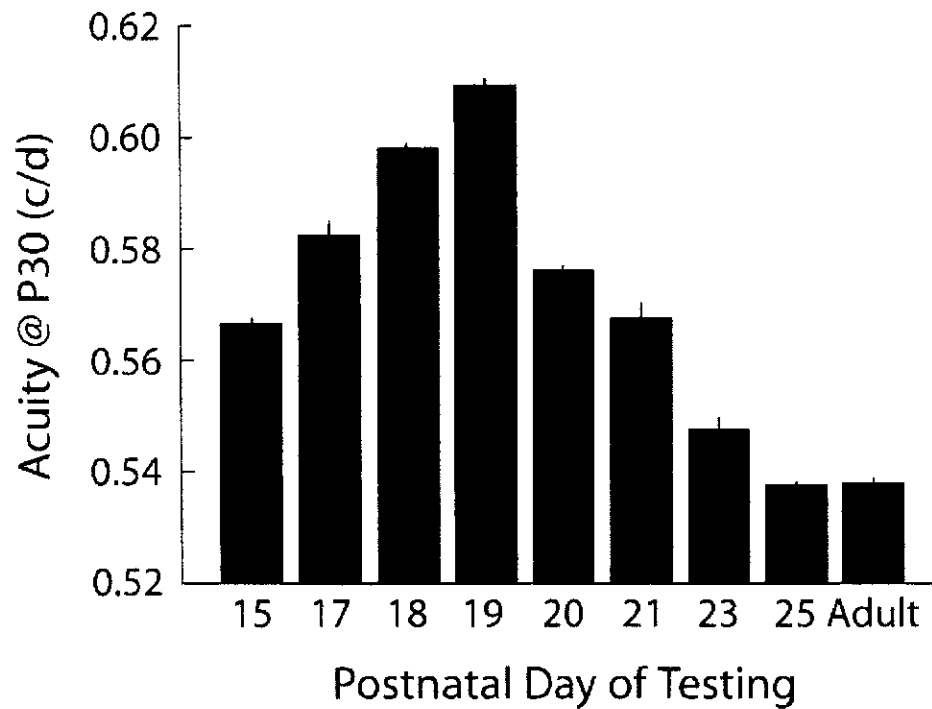


Figure 10. Profile of plasticity for optomotor enhancement. Animals were tested on only a single day between P15-P25 (P15, P17, P18, P19, P20, P21 and P23) and then measured daily after P25. Testing on P19 produced the largest enhancement in acuity (as measured on P30) accounting for ~25% of that obtained from testing each day from P15-P25 (0.86 c/d; from figure 9A). The plasticity is transient and is skewed toward younger ages. Values obtained by testing at P25 only did not differ from experimentally naïve animals (Adult; value from figure 3A). SEM is plotted as vertical lines on each bar. See text for details.

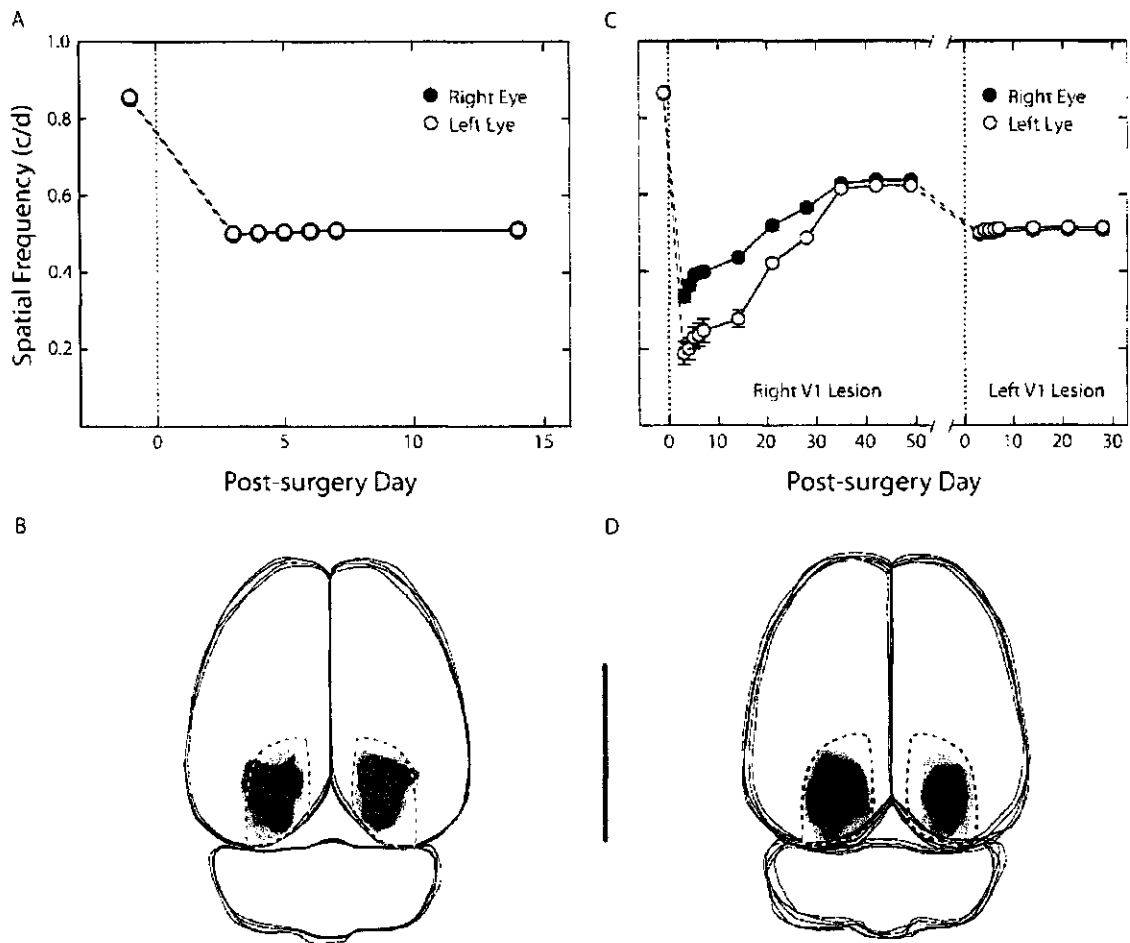


Figure 11. Enhancement of optomotor sensitivity is dependent upon primary visual cortex. **A**. Bilateral primary visual cortex lesions in animals tested in OptoMotry from P15 resulted in a large decrease in acuity through both eyes. Dotted line represents day of surgery. **B**. Traces of brains from animals in **A** superimposed on one another revealed that lesions were large and that little primary visual cortex remained intact. Dashed line represents the boundaries of primary visual cortex (Paxinos and Watson, 1998). Vertical calibration bar is 1 cm. **C**. Unilateral lesions of primary visual cortex made in sequence on animals tested from P15 resulted in a large decrease in acuity through both eyes. The dotted lines represent the two lesions. Unilateral lesions of right primary visual cortex resulted in a loss of acuity through both eyes. Acuity through the left eye was initially more affected than the right eye, but both recovered to the same intermediate values after 35 days. A subsequent lesion of left primary visual cortex resulted in a symmetric loss of acuity through both eyes to near experimentally naïve thresholds (refer to figure 3A). SEM bars are plotted but are smaller than most of the symbols. **D**. Traces of brains from animals in **C** showed that visual cortex lesions were virtually complete. See text for details.

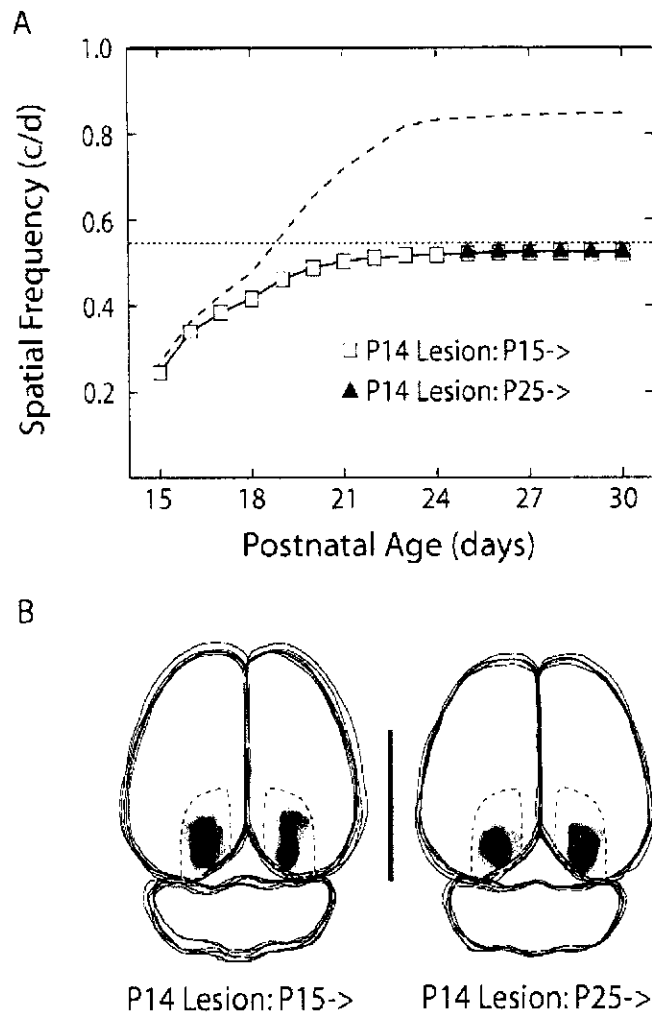


Figure 12. Bilateral primary visual cortex lesions the day before eye-opening (P14) block the characteristic enhancement of optomotor sensitivity. **A**. Following bilateral lesions animals were tested daily from eye-opening (P15->; open squares) or from P25 (P25->; solid triangles). Acuity did not differ between the lesion groups and was similar to intact naïve animals (dotted line is representative of P25-> trace from figure 8A). Dashed line is a trace from enhanced animals tested daily from P15 (P15-> from figure 8A). SEM is plotted but is smaller than the plotting symbols. **B**. Traces of brains from animals in **A** showed that visual cortex lesions were large and were centered in visual cortex. Dashed line represents the boundaries of primary visual cortex (Paxinos and Watson, 1998). Vertical calibration bar is 1 cm. See text for details.

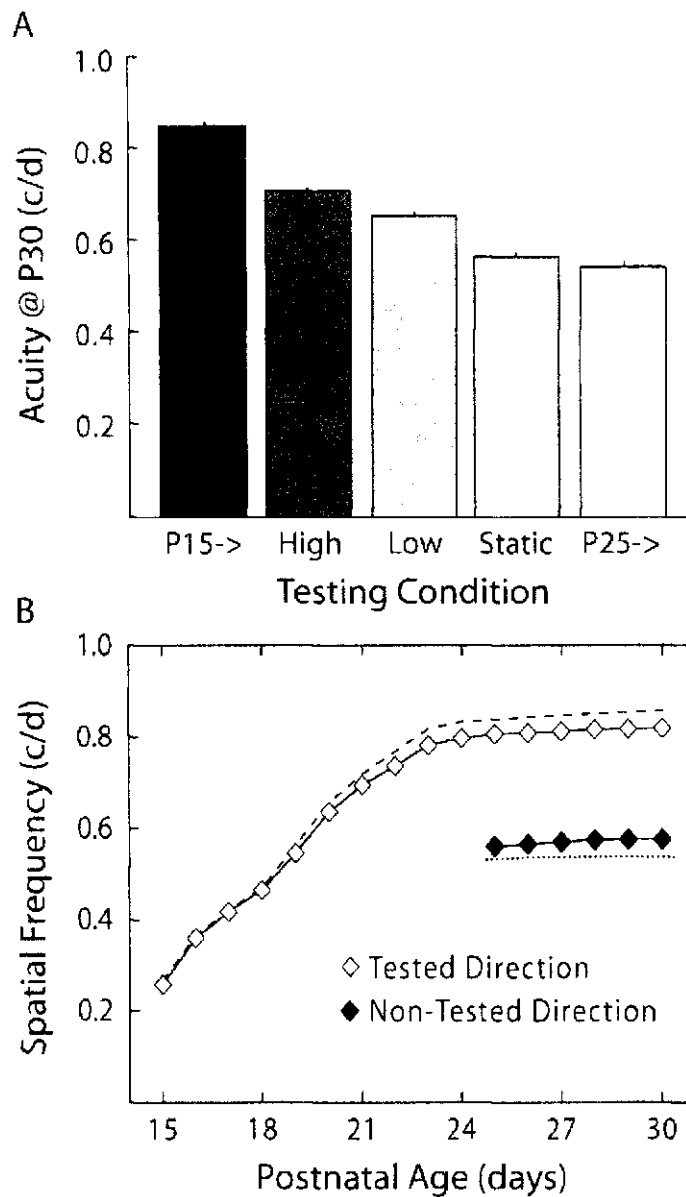


Figure 13. Experiential control of optomotor enhancement. **A.** Maximal optomotor enhancement resulting from daily testing from P15-P25 requires exposure to moving high spatial frequency stimuli that evoke tracking. Daily P15-P24 exposure to a high SPF (High) moving stimulus (0.83 c/d) that never generated tracking, or to a constant low SPF (Low) stimulus (0.03 c/d) that always generated tracking, did not result in maximal enhancement (P15-> trace from figure 8A). Experiencing stationary stimuli from P15-P25 (Static) resulted in only a small enhancement over animals not tested until P25 (P25-> threshold from figure 8A). Values plotted are from P30. SEM is plotted as vertical lines on each bar. **B.** Testing of each eye independently allows for within-animal control

of enhancement. Daily P15-P24 testing in one direction (open diamonds) resulted in near maximal enhancement (dashed line is P15-> trace from figure 8A) in the tested direction, and only a small enhancement (filled diamonds) in the non-tested direction (dotted line is P25-> trace from figure 8A). SEM is plotted, but is smaller than the symbols. See text for details.

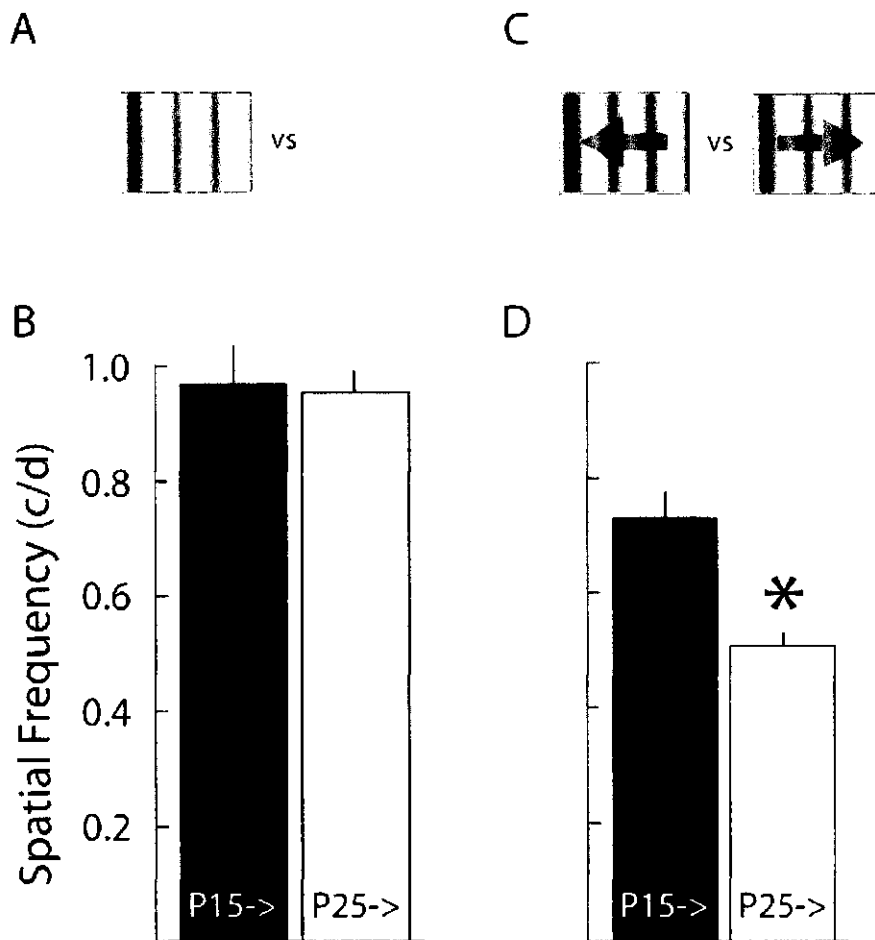


Figure 14. Testing the optomotor response from P15-P25 enhances motion perception. **A.** Static grey versus grating discrimination. The spatial frequency of a sine wave grating (+ stimulus) was increased until animals could no longer discriminate it from grey (- stimulus). **B.** Perception of static stimuli (A) is not enhanced by optomotor enhancement. Acuity of rats with optomotor experience from P15 (P15->) did not differ from that of animals with experience from P25 (P25->). **C.** Moving grating discrimination. The spatial frequency of identical sine wave gratings was increased until animals could no longer discriminate rightward moving (+ stimulus) from leftward moving (- stimulus) stimuli. **D.** P15-> rats were significantly superior to animals without the enhancement (P25->) at discriminating the spatial frequency of moving gratings (C). SEM is plotted as vertical lines on each bar. See text for details.

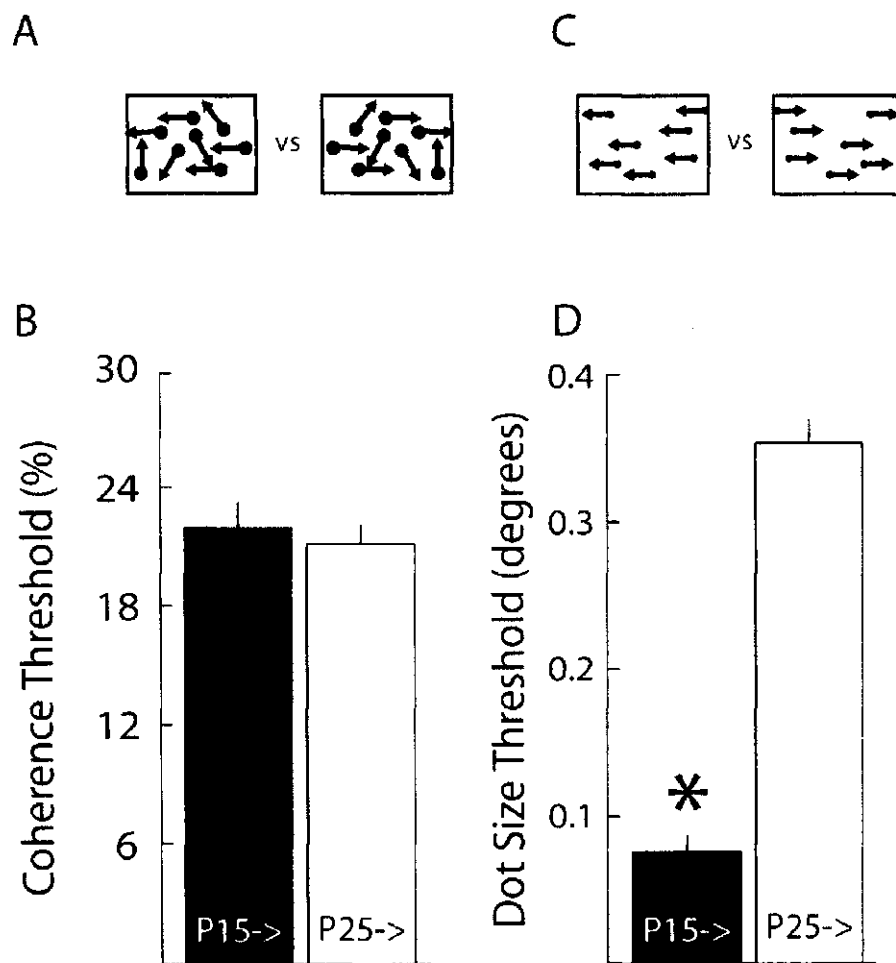


Figure 15. Perception of dot motion coherence. **A.** The coherence of identical dot kinematograms was decreased until animals could no longer discriminate rightward moving (+ stimulus) from leftward moving (- stimulus) stimuli. **B.** There was no difference in coherence thresholds between P15-> and P25-> animals when large dots (2.3°) were used. **C.** Animals discriminated between equal sized dots moving in the rightward (+ stimulus) and leftward (- stimulus) directions at 100% coherence. The size of the dots was decreased until animals could no longer discriminate between the screens. **D.** P15-> animals could discriminate significantly smaller dots than P25-> animals. SEM is plotted as vertical lines on each bar. See text for details.

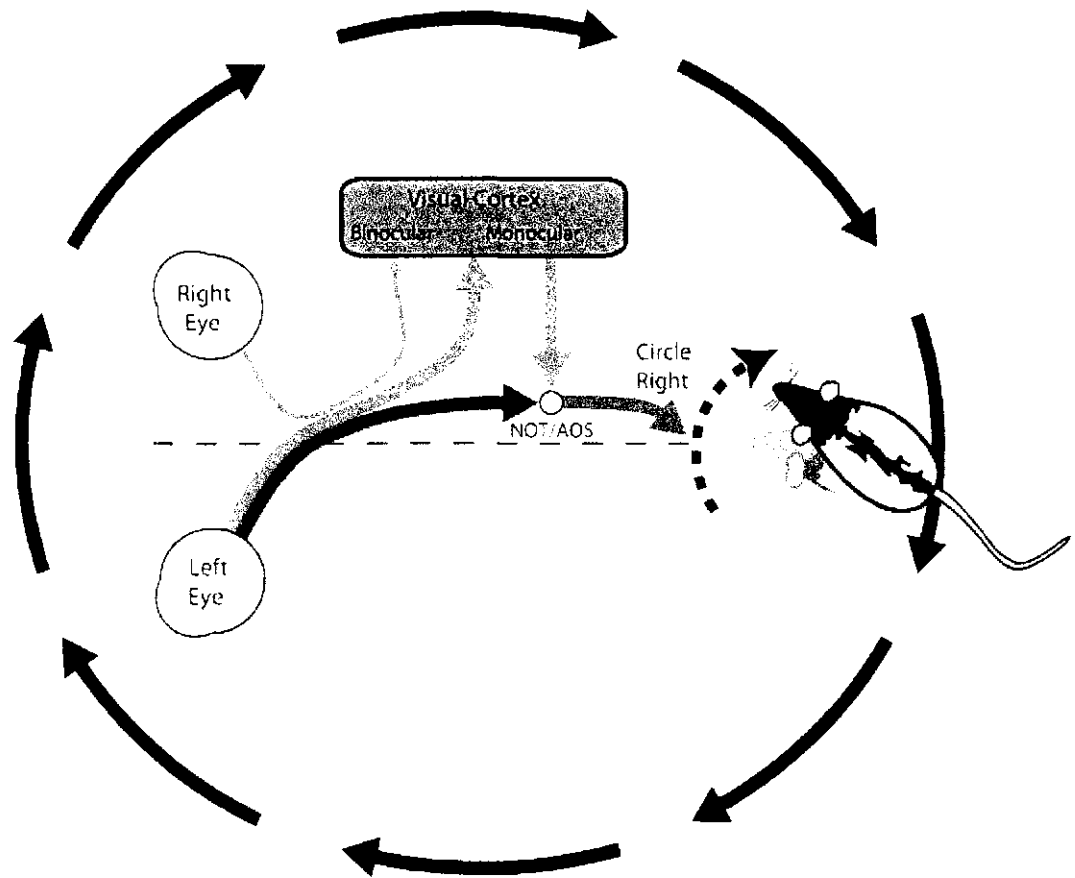


Figure 16. Model of the optomotor response in animals with enhanced acuity. Visual thresholds obtained from experienced animals with enhanced acuities reflect the properties of the retinal efferents (red arrows) and cortical projections (green arrows) to subcortical structures (open circle; NOT & AOS) unlike naïve animals where the cortico-subcortical projection has no effect on optomotor sensitivity (Refer to figure 8). Adapted from SFN poster, Douglas *et al.*, 2005.

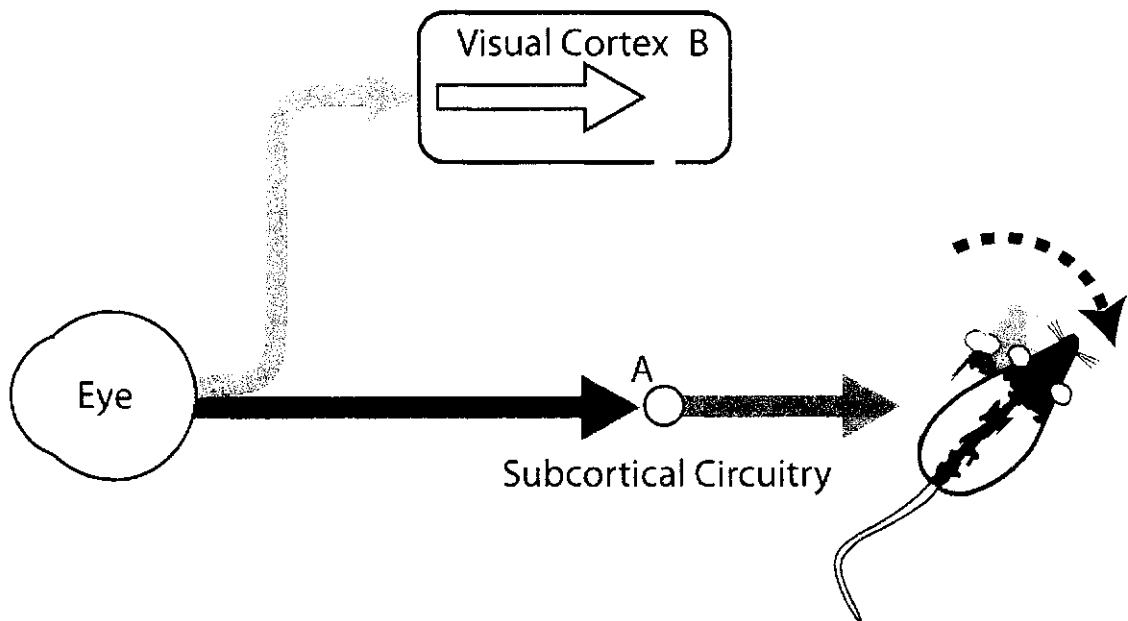


Figure 17. Possible sites of plasticity for visual motion enhancement. Plasticity may occur where the cortical input (green arrow) synapses onto the nuclei of the subcortical circuitry responsible for generating the optomotor response (site indicated by 'A'). The second location of plasticity may be in the cortex (site indicated by 'B'), which then has downstream effects on the subcortical nuclei. Alterations at either, or both sites, may result in enhanced responses to high spatial frequency moving stimuli. See text for details.

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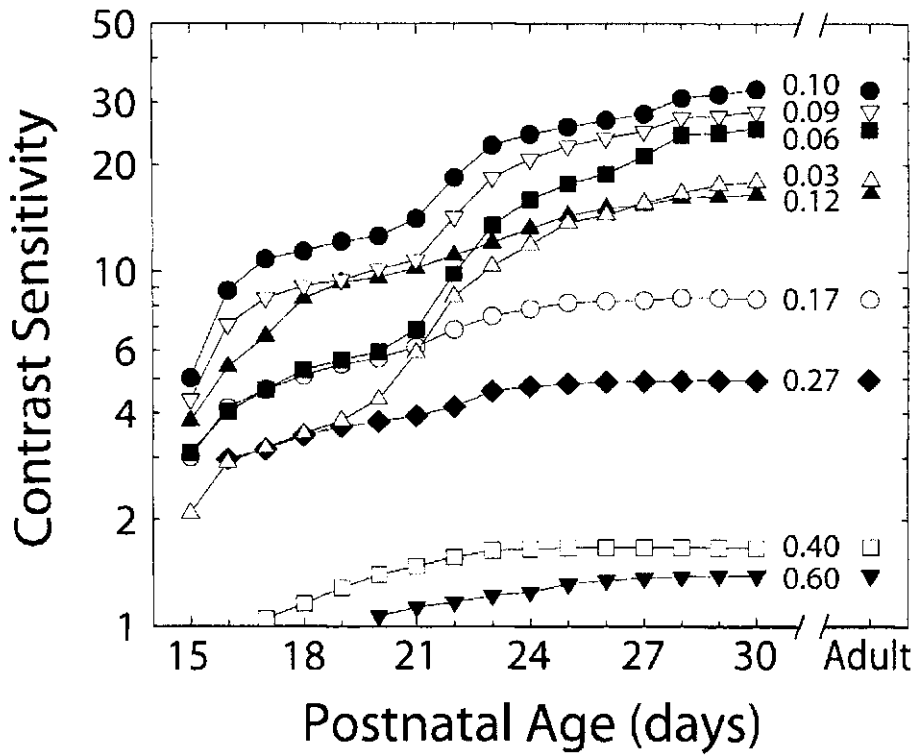
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Appendix A. Contrast Sensitivity of developing Long-Evans rats over time. At all spatial frequencies tested the contrast sensitivity increased from eye-opening to ~P30 and remained unchanged into adulthood. Differential development of several spatial frequency channels occurred, some of which were similar. Values within the box represent the spatial frequency corresponding to each symbol and line. SEM is plotted, but is smaller than the symbols. See text for details.