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2-Deoxyglucose Analysis of the Neonatal and Adult Guinea Pig Visual Systems

by

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A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE

DEGREE OF MASTER OF SCIENCE

CALGARY, ALBERTA

APRIL, 1994

ISBN 0-315-93905-2

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The undersigned certify that they have read and recommended to the Faculty of Graduate Studies for acceptance, a thesis entitled, "2-Deoxyglucose Analysis of the Neonatal and Adult Guinea Pig Visual Systems," submitted by Eleanor Gail Hamaluk in partial fulfillment of the requirements for the degree of Master of Science.

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ABSTRACT

The visual system of the precocial guinea pig was examined using the 2-deoxyglucose autoradiographic technique. Adult, and visually inexperienced 1 day and 13 day old guinea pigs were monocularly exposed to either patterned or diffuse visual displays illuminated by either steady or flashing light. Metabolic activity was assessed in the visual cortex, lateral geniculate nucleus, and superior colliculus. In support of Hubel and Wiesel's (1963) contention that nature defines the response properties of visual cells, visual cells of the newborn guinea pig showed mature metabolic activity at the time of eye opening. A similar pattern of metabolic activity was found across all test conditions in all three age groups. Striped stimuli elevated the metabolic response of neurons in the visual cortex of all age groups while diffuse light had little or no effect on glucose metabolism. In agreement with previous research these findings demonstrate that the cortex processes information about variations in spatial patterns rather than diffuse light. Subcortical structures paralleled the cortex in their metabolic response to contoured stimuli. High contrast contours maximally increased carbon-14 uptake in the thalamus and colliculus of adult and visually inexperienced animals. Diffuse illumination, however, increased thalamic activity while it suppressed superior colliculus activity.

ACKNOWLEDGEMENTS

I would like to express my gratitude to my advisor Dr. R. M. Cooper for his assistance throughout all portions of this thesis. I would also like to thank Dr. Spira for contributing a number of the guinea pigs used in this experiment.

I would also like thank my parents, Keith and Lorraine for their ongoing love and support.

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CHAPTER 1

INTRODUCTION

1.1 Overview

There is substantial disagreement among researchers over the degree to which the environment and heredity influence visual development. One strategy used to determine the contributions of heredity and the environment to visual development has been to compare the response properties of the visual system of the newborn to those of the adult. Results from such studies are contradictory. Some researchers have concluded that the visual system is mature at the time of eye opening (Hubel & Wiesel, 1963; Sherk & Stryker, 1976; Wiesel & Hubel, 1974), others have concluded it is not, suggesting that environmental input is required for normal development (Blakemore & Van Sluyters, 1975; Barlow & Pettigrew, 1971; Imbert & Buissert, 1975; Pettigrew, 1974). The latter researchers have argued that plasticity in the visual system is essential as it promotes the formation of functionally appropriate connections, ensuring that the organism is best adapted to the environment.

Visual deprivation studies show that the system can be modified by the environment. However, it is difficult to determine whether changes following deprivation are due to the formation of new cellular receptive field properties or simply a degeneration of pre-existing cellular receptive field properties.

The objective of this study was to use the 2-deoxyglucose method to examine whether the visual systems of adult, 1 day, and 13 day old precocial guinea pigs were similar. Studies which have compared the visual system of adult and newborn animals are discussed in section 1.2 of the thesis. A literature review summarizing the effects of deprivation on cortex, lateral geniculate nucleus and superior colliculus anatomy and function is given in sections 1.3 through 1.6. Sections 1.7 and 1.8 deal with previous 2-deoxyglucose work on the rat and the anatomy of the guinea pig visual system.

1.2 Studies of the neonatal visual system

The relative contributions of nature and nurture to visual system development has been of great interest to neuroscientists. After examining the visual system at the time of eye opening, to assess the level of developmental maturity, some studies have suggested that the neonatal visual system is functionally adult-like (Hubel & Wiesel, 1963; Sherk & Stryker, 1976; Wiesel & Hubel, 1974). Other studies however, have suggested that the neonatal visual system is not functionally adult-like at the time of eye opening, rendering it conceivable that visual experience after eye opening could be important to normal maturation of the system (Barlow & Pettigrew, 1971; Blakemore & Van Sluyters, 1975; Imbert & Buissert, 1975; Pettigrew, 1974).

Hubel and Wiesel's (1963) seminal work suggested that the visual system of the newborn was fully mature, developing in

the absence of visual input. Extracelluar recordings from the cortex of 8, 16, 19 and 21 day old kittens identified cells with receptive fields characteristic of the normal adult cat. Cells responded only when presented with bars or slits of light and could not be driven by diffuse illumination. As in visual cells of the adult cat the neonatal cortical cells were orientation selective, responding to an edge only if it fell within a narrow range of angles. Finally, cells in both the adult and the newborn cat had a similar ocular dominance distribution and were organized into columns in which functionally related visual cells aggregated together.

In contrast to Hubel and Wiesel, other investigators reported that cells in the visually inexperienced cat's striate cortex were not mature at birth. Some investigators reported that cells in the neonate cortex lacked mature receptive fields and concluded that visual experience was necessary for the development of specific response properties in visual cortical neurons (Barlow & Pettigrew, 1971; Imbert & Buissert, 1975).

Pettigrew (1974) failed to find neurons from the immature cortex which were orientation selective. Recording from visual cortical cells in normally reared kittens, Buissert and Imbert (1974) found that between the 8th and 11th postnatal day most neurons were visually non-responsive although by the 29th to 42nd day cells responded with adult-like receptive fields. In agreement with these findings Freqnac and Imbert (1978) and

Tsumoto and Suda (1982) reported that a large portion of cortical cells remained unresponsive to visual stimulation during the first postnatal weeks.

Albus and Wolf (1985) examined the columnar organization of cells in visual cortex of the newborn kitten and reported that at birth orientation columns were not present. Thompson, Kossut and Blakemore (1983) used the 2-deoxyglucose technique to study the emergence of orientation dependent columnar organization in the cortex of kittens exposed to horizontal gratings. At 14 days postnatal, consistent with the findings of Albus and Wolf, no regular columns of differential labelling were detectable in striate cortex but by the fourth postnatal week labelling in the cortex paralleled that found in the adult cortex.

Differences between adult and newborn animals also became apparent when researchers examined layer IV of the cortex. Some studies suggested that at the time of birth ocular dominance columns were not fully formed. In newborn kittens and monkeys it appeared that extensive overlap occurred in the arborization of geniculate fibres, representing both eyes, which ended in layer IV (Le Vay, Stryker & Shatz, 1978). Instead of being restricted to separate cortical areas, as in the adult, the arborization spread over a wide area so that cells were driven by both eyes. During the first six weeks the arborization retracted so that cells were supplied by one eye or the other and as in the adult could only be driven by a

single eye. This implied that development of the visual system continues after birth for an extended period of time.

The literature clearly demonstrates a lack of agreement about which features of the basic wiring necessary for mature vision are already present at birth and which become fully developed only in the first few weeks of life. According to Hubel and Wiesel (1963) neurons show adult-like receptive field properties in the absence of experience, whereas according to Pettigrew (1974) neuronal response selectivity is not present in the newborn kitten. The conflicting findings have led many researchers to investigate whether the response properties of cells in the visual system are modifiable in early life.

The influence of monocular and binocular deprivation and restricted visual environments on cortical, lateral geniculate nucleus and superior colliculus neuronal function are described in the following section. In general, the neurons of the visual system are susceptible to change early in life. Deprivation reduces the ability of the deprived eye to drive visual cells, with the changes being most pronounced in the visual cortex, although the lateral geniculate nucleus and superior colliculus cells may be affected.

1.3 Visual cortex deprivation studies

Area 17: Monocular deprivation

Extensive physiological changes can be found in the visual cortex of animals monocularly deprived of visual input.

In kittens monocularly lid-sutured from birth, the majority of excitable cortical cells are driven exclusively by the non-deprived eye, with only 5-10% of the cells being activated by the deprived eye (Hubel & Wiesel, 1970; Singer, 1977; Wiesel, 1982; Wiesel & Hubel, 1963b; Wiesel & Hubel, 1965b; Wilson & Sherman, 1977). Moreover, an abnormally large number of cells are unresponsive to visual stimulation as compared to the non-deprived adult cat in which it is possible to drive all cortical cells with the appropriate visual stimuli (Hubel & Wiesel, 1963; Wiesel & Hubel, 1963b). Of the few cortical neurons that could be driven by the deprived eye most showed abnormal receptive field properties. Generally, the response of the cell is weak, inconsistent and lacks orientation or directional selectivity (Fregnac & Imbert, 1984; Spear, Langsetmo, & Smith, 1980; Wiesel & Hubel, 1965b). Similarly, the majority of cells in the monkey striate cortex are driven by the non-deprived eye following monocular deprivation (Carlson, Hubel & Wiesel, 1986).

The number of cells which cannot be activated or have abnormal receptive fields is proportionally higher in the binocular segment of the cortex where the effect of monocular deprivation is more severe when compared to the monocular segment. In the monocular segment over 52% of the cells will respond to stimulation of the deprived eye with normal receptive field properties, whereas in the binocular segment only 1% respond (Watkins, Wilson & Sherman, 1978).

Interest arose in possible morphological changes that might underlie the physiological abnormalities of cortical neurons in monocularly deprived animals. Studies show that some neuronal input to the cortex from the deprived eye remains excluding the possibility that neuronal non-responsiveness is due to the complete elimination of geniculocortical inputs from the deprived eye (Shatz & Stryker, 1978). Gary and Blakemore (1977) injected horseradish peroxidase (HRP) into the striate cortex of kittens which resulted in retrograde labelling of lateral geniculate nucleus cells in the laminae receiving projections from the deprived eye. Comparable findings were obtained by Lin and Sherman (1978) who found HRP labelled projections from the deprived cortex to the lateral geniculate nucleus were reduced in number but still present. Following unilateral injections of HRP into area 17, 77% of the cells in nondeprived laminae were labelled while 11% fewer cells, 66%, were labelled in deprived laminae.

In addition to reduced numbers of geniculocortical inputs following deprivation, a marked reduction in the width of the ocular dominance columns that received input from the deprived eye occurs (Hubel, Wiesel & Le Vay, 1977). This is accompanied by a corresponding increase in the size of the ocular dominance columns receiving normal eye input.

The existence of neuronal input from the deprived eye to cortical cells may explain the paradoxical findings obtained

by Cooper, Thurlow, Jeeva and Gafka (1992) while using 2-deoxyglucose to examine the effects of monocular deprivation on cortical neurons in the rat. In this study the uptake of 2-deoxyglucose was found to be substantially greater in the hemisphere receiving input from the visually deprived eye as compared to the non-deprived eye. Greater 2-deoxyglucose uptake in the deprived cortex was also demonstrated to be age dependent, occurring only in rats which received early monocular deprivation. Electrophysiological work would predict increased metabolic activity in the non-deprived hemisphere paralleling the increased capacity of the non-deprived eye to drive the visual system following monocular deprivation. The authors suggest that early monocular deprivation increased the capacity of the deprived eye to activate the visual system by responding indiscriminately to many spatial features of light and henceforth causing cells receiving input from this eye to be more metabolically active than selective non-deprived cells.

It is not known why cells are primarily driven by the non-deprived eye following monocular deprivation although input from the deprived eye to the cortex remains. It has been suggested that the non-deprived eye suppresses input from the deprived eye to cortical neurons (Sclar, Ohzwaw, Freeman, 1986; Kratz, Spear & Smith, 1976). In support it has been demonstrated that both intravenous injection (Duffy, Snodgrass, Burchfiel, & Conway, 1976) and iontophoretic

cortical application (Burchfiel & Duffy, 1981) of the Gamma-aminobutyric acid (GABA) antagonist, bicuculline, restored the ability of the deprived eye to drive cortical cells. GABA is thought to be an inhibitory neurotransmitter in the visual cortex (Duffy et al., 1976). If the non-deprived eye caused the inhibitory transmitter, GABA, to suppress synaptic input from the deprived eye a reduction of this synaptic inhibition would lead to restoration of the deprived eye's ability to drive cortical cells. Intracortical inhibitions may then play a role in maintaining shifts in ocular dominance produced by monocular deprivation.

Following deprivation the majority of cortical cells are driven exclusively by the non-deprived eye, the effect being most pronounced in the binocular segment of area 17. It appears that geniculocortical input from both eyes are competing for representation in the visual cortex and that deprivation disrupts the balance established between the eyes allowing the non-deprived eye to become dominant. Monocular deprivation demonstrates the importance of normal vision in both eyes to the maintenance rather than the formation of normal ocular dominance in the cortex.

Area 17: Binocular deprivation

Deprivation of visual input to both eyes is most commonly achieved through binocular lid-suture or dark rearing. Dark rearing eliminates all light stimulation while binocular lid-suture reduces the intensity of illumination reaching the

retina and deprives the eye of all patterned stimulation. Despite the different nature of visual deprivation achieved by either method research suggests that their general effect is similar on cortical area 17 (Blakemore & Van Sluyters, 1975).

Both binocular lid-suture and dark rearing result in a visual cortex which is less responsive than normal to visual stimulation. In the monocular and binocular segments of cortex there is a reduction of the number of cells responsive to light stimulation (Blakemore & Van Sluyters, 1975; Buissert & Imbert, 1976; Fregnac & Imbert, 1978; Freeman & Ohzwa, 1988). The percentage of non-responsive neurons found after binocular deprivation varied from as high as ~40% (Buissert & Imbert, 1976) of the total number of units studied to as low as ~20% (Watkins, Wilson & Sherman, 1978), with the reported percentage of visually unresponsive cells increasing as the length of deprivation increased.

Similarly, the proportion of neurons with non-specific receptive fields increased with the duration of deprivation (Buisseret & Imbert, 1976; Fregnac & Imbert, 1978).

Non-specific cells responded to moving stimuli with no clear preference for direction of the movement (Kratz & Spear, 1976; Watkins et al., 1978) and failed to show orientation selectivity (Buissert & Imbert, 1976; Fregnac & Imbert, 1978; Imbert & Buissert, 1975; Freeman & Ohzawa, 1988). Cells with non-specific receptive fields tended to be binocularly activated (Blakemore & Van Sluyters, 1975; Kratz & Spear,

1976; Leventhal & Hirsch, 1980; Watkins et al. 1978). These cells appear to be similar to those found in the cortex of the newborn kitten in which cells are driven by both eyes, rather than a single eye. It is possible then, that binocular deprivation arrests development of some cells leaving them in an immature state.

Non-specific cells also had abnormal binocular interactions. In normal cats a small change in the retinal disparity of an image falling on each retina can lead to inhibition of the neuronal response. Cells in the deprived cat, however, were insensitive to changes in retinal disparity (Nikara, Bishop & Pettigrew, 1968). Thus the neuron's rate of firing was unaffected by misalignments between the two stimuli presented to the retina.

Despite the existence of abnormal cells, a larger percentage of cells display normal receptive fields following binocular lid-suture than following monocular lid-suture. In addition, most studies reported normal ocular dominance among responsive cells after dark rearing or binocular deprivation (Buisseret & Imbert, 1976; Fregnac & Imbert, 1978; Imbert & Buisseret, 1975; Wiesel & Hubel, 1965b). Unlike in monocular deprivation, neither eye has an advantage over the other during binocular deprivation allowing a normal columnar structure to develop.

In summary, despite normal ocular dominance organization and a large number of normal cells following binocular lid-

suture some cells are non-responsive or display abnormal receptive field properties. It can be concluded that some but not all of the effects of closing one eye during deprivation can be reduced by closure of both eyes.

Area 17: Restricted visual environments

After examination of the effects of monocular and binocular deprivation the next question for many researchers was whether cortical response properties could be modified using a restricted visual environment. Extensive study of deprivation of both movement and orientation selectivity in cortical neurons has produced few firm conclusions. These investigations plus experiments which reared animals in strobe light will be reviewed.

Most researchers agree that the distribution of orientation preferences found in cortical cells can be modified by visual experience which is restricted to contours of a single orientation (Blakemore & Mitchell, 1973; Blakemore, Movshon & Van Sluyters, 1978; Blasdel, Mitchell, Muir, & Pettigrew, 1975; Hirsch & Spinelli, 1970; Pettigrew, Barlow & Olson, 1973; Pettigrew & Garey, 1974; Pettigrew, Olson & Hirsch, 1973; Spencer & Coleman, 1974; Spinelli & Hirsch, 1971; Tretter, Cynader & Singer, 1975). Hirsch & Spinelli (1971) exposed dark reared kittens, three weeks of age, to vertical or horizontal stripes using goggles which prevented binocular vision. One eye was exposed to alternating black and white vertical lines the other alternating black and

white horizontal lines. After 504 hours of restricted visual exposure the receptive fields of units recorded from the cortex showed a preference for stimuli oriented either vertically or horizontally; cells with vertically oriented receptive fields were driven exclusively by the eye exposed to vertical lines and cells with horizontally oriented receptive fields were driven exclusively by the eye exposed to horizontal lines. The lack of binocularly activated cells is unusual, normally 80-90% of the cells in the visual cortex can be stimulated by both eyes and may be explained by the absence of binocular exposure to visual stimuli. Allowing normal binocular vision, Blakemore and Cooper (1970), also reared kittens in an environment with horizontal or vertical stripes. To achieve this the kittens were placed in a cylinder, the inside of which was covered in vertical or horizontal stripes, for 5 hours per day for up to 5 months. Approximately 75% of the units tested were preferentially activated by horizontal or vertical stimuli at the end of the 5 month period.

Stryker and Sherk (1975), however, were unable to reproduce the results obtained by Blakemore and Cooper (1970). Orientation-tuning histograms of cells exposed to horizontal or vertical stripes for 300 hours showed no tendency for units to be more selective for the orientation viewed during rearing. Cortical organization of orientation columns was the same as that found in normal cats. Stryker, Sherk and Leventhal (1978) also made use of the rearing procedure

described by Hirsch and Spinelli (1971) to examine the consequences of restricted visual experience on the cortex. Unlike the results obtained by Hirsch and Spinelli, up to 54% of cortical cells were nonselective for orientation or completely unresponsive to visual stimulation. Only 25% of cells showed some bias toward the orientation viewed during rearing, although these cells responded more erratically and to a broader range of orientations than did cells in normal cats.

The large percentage of non-responsive cells suggest that degeneration of certain cortical neurons occurred. Visual cortex cells did not appear able to adjust their receptive field properties to match the environment. The results were consistent with the idea that early visual experience plays a role in maintaining pre-existing innate selectivity in cortical cells rather than determining the distribution of preferred orientations, as a large percentage of cells are completely unresponsive to stimuli regardless of their orientation.

Relatively few studies have addressed plasticity of direction selectivity in the visual cortex. Available evidence suggests that direction selectivity of cells can be modified. (Daw, Berman & Ariel, 1978; Daw & Wytt, 1976). Raising kittens in an environment with stripes moving in a single direction leads to the majority of cells preferring movement in the experienced direction (Daw & Wyatt, 1976; Tretter, Cynader &

Singer, 1975). Evidence suggests that there is a critical period in which direction selectivity of cortical cells can be modified. When the direction of movement viewed is reversed after 7 weeks 90% of the cells preferred the direction initially viewed, whereas when the direction of movement viewed is reversed after 5 weeks only 70% of the units recorded prefer the direction initially viewed (Berman & Daw, 1977; Daw & Ariel, 1980; Daw & Wyatt, 1976).

An alternate approach to studying direction selectivity of cortical cells is through the use of strobe-rearing. Strobe-rearing differs from unidirectional rearing studies in that the flashing contours produced by the strobe is equivalent to the complete deprivation of motion. Strobe rearing might therefore be expected to have the greatest effect on neurons devoted to motion analysis. Binocular strobe rearing results in a dramatic reduction in the number of direction selective cells present in the visual cortex (Kennedy & Orban, 1983; Pasternak, Schumer, Gizzi, & Movshon, 1985; Pasternak, Movshon, & Merigan, 1981; Rauschecker & Schrader, 1987). Behaviorally, strobe-reared cats differ from normally reared cats. When required to discriminate between two patterns moving at the same speed in opposite directions strobe reared cats responded correctly only when pattern contrast was 10 times higher than the contrast of patterns shown to normal cats (Pasternak & Leinen, 1986).

In summation, the receptive field properties of cortical

cells could not be completely re-shaped under controlled environmental conditions. These studies show that whereas a minority of cells do display properties that match the environment viewed, many became unresponsive and would not respond to any visual stimuli. It could be concluded that nature establishes a precise range of probable receptive field properties that a cell might display. The environment may select from this narrow range of probable phenotypes but it can not determine them. Should the environment be so abnormal that none of a cells genetically determined phenotypes can be expressed the cell will become non-responsive as it is unable to generate new receptive field properties to match the abnormal environment.

1.4 Lateral geniculate nucleus deprivation studies

Lateral geniculate nucleus: Monocular deprivation

In the lateral geniculate of the adult cat there are three well defined layers, lamina A, lamina A1 and lamina C, one of which, layer C, has been further sub-divided into C, C1 and C2. In addition two functionally distinct types of cells are present in the geniculate, X or sustained cells and Y or transient cells. Anatomical studies have shown that layers A, and A1 of the geniculate are supplied by only one eye (Kuffler & Nicholls, 1976). Wiesel and Hubel (1963a) were the first to examine the effects of monocular deprivation on the geniculate. In contralateral lamina A and ipsilateral lamina A1, innervated by the deprived eye, cells were found to be

one-third smaller than cells receiving normal retinal input. Despite the reduction in size the cells recorded from layer A and A1 were described as having essentially normal receptive fields. The reduction in mean soma size in deprived geniculate laminae was subsequently supported (Guillery, 1973; Guillery & Stelzner, 1970; Hickey, Spear & Kratz, 1977; Lin & Sherman, 1978; Mangel, Wilson & Sherman, 1983) as was the existence of normal receptive fields following monocular deprivation (Guillery & Stelzner, 1970; Sherman, Hoffman & Stone, 1972). Guillery & Stelzner (1970) noted that abnormalities in soma size and density were restricted to the binocular segment of lamina A.

Guillery (1972) later showed that abnormal geniculate cell growth occurs through binocular competition. In an ingenious experiment Guillery created a monocular segment in normally binocular lamina, through the destruction of a portion of temporal non-deprived retina in a monocularly lid-sutured animal. As predicted, the binocular segment of geniculate lamina A1 contralateral to the lid-sutured eye showed neuronal degeneration. The portion of binocular segment innervated by the patch of destroyed retina, however, did not show cell atrophy because these cells were innervated exclusively by the deprived eye therefore no other retinal inputs were present to compete during development.

When cell type is considered, research indicates that visual deprivation results in a selective loss of Y-cells from

layers A and A1 of the lateral geniculate nucleus in addition to a reduction in Y-cell soma size (Hoffman & Hollinder, 1978; Frankle, Blakemore & Wolfe, 1979; Friedlander et. al., 1982; Friedlander & Stanford, 1982; MacAvoy, Salinger & Garraghty, 1990; Sherman et al., 1972). Mangel et al. (1983) measured a significant decrease in the proportion of Y-cells in deprived lamina A and A1 as compared to non-deprived lamina of cats after 24 weeks of deprivation. No difference in the response properties of Y-cells in the deprived and non-deprived lamina were found. Although no difference in the proportion of X-cells has been reported, deprivation does affect the response properties of this class of cells (Christen & Mower, 1987; Maffei & Fiorentini, 1976; Mangel et al., 1983; Sireteanu & Hoffman, 1979).

Hickey (1980) examined laminae C of the kitten using autoradiographic techniques following monocular deprivation which began at birth. Significant decreases in cell size occurred in deprived laminae C beginning at day 28; before this time cells in deprived and non-deprived laminae C showed only increases in size. In layer C, despite changes in soma size, the proportion and receptive field properties of Y and W cells were unaffected by deprivation as evidenced by their similarity in the deprived and non-deprived lamina (Spear, McCall & Tumosa, 1989).

Studies aimed at determining whether lateral geniculate cell size changes are due to an arrest in cell growth or are

due to cell atrophy suggest that deprivation affects developing lateral geniculate neurons by altering cell growth rather than through atrophy (Hickey, 1980; Kalil, 1980).

In the primate the morphological effects of monocular deprivation parallel those found in the cat. Both magnocellular and parvocellular cells in the geniculate were smaller than their non-deprived counterparts (Casagrande & Joseph, 1980). Deprived arbors of parvocellular and magnocellular cells were altered in shape, smaller in area, and had fewer buttons (LaChica, Crooks & Casagrande, 1990). Despite cell size changes, the receptive field properties of all geniculate cells were physiologically normal following deprivation in the primate (Blakemore & Vital-Durand, 1986).

In summation, monocular deprivation of the LGN primarily leads to a reduction of Y-cell soma size in the binocular segment of the geniculate, receptive field properties however, are unchanged. In addition, a selective loss of Y-cells has been reported. The proportion of X-cells on the other hand, may be unaffected by deprivation although their receptive fields are abnormal.

Lateral geniculate nucleus: Binocular deprivation

Wiesel and Hubel (1965a) and (1965b) reported cell soma in the geniculate were equally reduced in size following binocular lid-suture as they were after monocular lid-suture. Deprived soma showed a 40% reduction in size when compared with soma in non-deprived cats. In contrast, Hickey et al.,

(1977) and Guillery (1973) have shown a much smaller reduction in cell size following binocular lid-suture, only 5-12%. As with monocular deprivation, binocular deprivation results in fewer Y-cells in the lateral geniculate nucleus (Frankle, Blakemore, & Wolfe, 1979; Mower, Burchfiel, & Duffy; 1981; Sherman, et al., 1972; Kratz, 1981). Unlike monocular lid-suture however, binocular deprivation affects the monocular and binocular segments of geniculate lamina A and A1 equally (Sherman et al., 1972). Although reduced in size and proportion Y-cells show normal receptive fields (Kratz, 1981). The frequency of lateral geniculate X-cells is unaffected by light deprivation. X-cells are present in normal ratios in both the monocular and binocular geniculate segments and develop normal receptive field properties (Derrington & Hawken, 1981; Mitchell, 1988; Mower et al., 1981; Sherman et al, 1972).

In summary, direct comparisons between deprived lamina in the geniculate of monocularly or binocularly lid-sutured kittens reveal a greater reduction in soma size following monocularly deprivation. However, both result in a reduced proportion of Y-cells with normal receptive field properties.

Lateral geniculate nucleus: Restricted visual environments

Few studies have examined lateral geniculate cells after animals have been reared in restricted visual environments. Daniels, Normal, and Pettigrew (1977) found an increase in the

number of lateral geniculate cells with orientation biases either parallel or orthogonal to the orientation of the stripe viewed during rearing. In contrast, Rauschecker (1984) noted that kittens reared with lenses designed to restrict vision in one eye to contours of a single orientation showed no preference for the experienced orientation at the level of the lateral geniculate nucleus.

As with the cortex the effects of rearing animals in restricted viewing environments are not conclusive, the receptive field properties of LGN cells may be alterable but not to the degree that one would expect if the environment was responsible for determining their properties.

1.5 Superior colliculus deprivation studies

Superior colliculus: Monocular deprivation

The superior colliculus of the cat can be partitioned into seven distinct layers. The upper three layers receive direct retinal input and input via the lateral geniculate nucleus and visual cortex. The retinal pathways to the colliculus are composed of extensive direct projections from W-cells, and minor direct projections from Y-cells (Hoffmann & Sherman, 1974; Kornguth, Spear, & Langer, 1982; Spear, Jones, Zetlan, Geisert, & Kornguth, 1982). An indirect Y-cell pathway also projects to the colliculus. The indirect Y-cell pathway is described as following this chain of neurons and synapses: retinal Y-cell input to the lateral geniculate nucleus Y-cells which project to the visual cortex complex

cells which project to collicular cells (Crabtree, Spear, McCall, Jones, & Kornguth, 1986; Hoffman & Sherman, 1974). The distinction between direct Y-cell retinal and indirect Y-cell cortical input to the colliculus is important as monocular and binocular deprivation affect input from each pathway differently (Berman & Sterling, 1976; Hoffman & Sherman, 1974).

Following deprivation the majority of superior colliculus cells responded exclusively to the normal eye and are described as directionally selective with normal receptive fields (Berman & Sterling, 1976; Wickelgren & Sterling, 1969). Of the small proportion of cells which responded to the deprived eye few are direction selective (Berman & Sterling, 1976; Hoffman & Sherman, 1974).

Wickelgren and Sterling (1969) studied the responses of colliculus cells in monocularly deprived kittens before and immediately following cortical removal. Recordings made after cortical lesioning showed that most cells now responded to visual stimulation of the deprived eye. This suggests that retinal input to the superior colliculus from the deprived eye is suppressed by cortical input (Berman & Sterling, 1976).

Superior colliculus: Binocular deprivation

Several studies have investigated the effects of binocular deprivation on the superficial layers of the superior colliculus in the cat. Binocular deprivation leads to a reduction in the proportion of direction sensitive cells.

Estimates vary from study to study from as high as a 78% reduction in direction sensitive cells (Crabtree, Spear, McCall, Jones, & Kornguth, 1986) to a low of 45% (Rauschecker & Harris, 1983). Changes in ocular dominance were also found in deprived cells. Colliculus cells in the normal cat were driven quite equally by either eye whereas the contralateral eye dominates in the binocularly deprived cat's colliculus (Hoffman & Sherman, 1974; Rauschecker & Harris, 1983). In addition, Rauschecker and Harris (1983) found a large number of units completely unresponsive to visual stimulation in the deprived colliculus.

When the direct retinal and indirect cortical inputs to the colliculus are considered three conclusions have been drawn. Binocular deprivation produced a moderate loss of Y-cell direct input, a severe loss of Y-cell indirect input and no change in W-cell input. The changes in colliculus input were thought to parallel deficits in the binocularly deprived lateral geniculate nucleus (Crabtree et al., 1986; Hoffman & Sherman, 1974).

1.6 Summary

In conclusion, monocular deprivation leads to the majority of cells being driven exclusively by the undeprived eye. This is accompanied in the cortex by a reduction in the width of ocular dominance columns usually supplied by the deprived eye, suggesting that competition occurs between the two eyes for representation in the visual structures. In

support of this hypothesis binocular deprivation results in an increase in the number of unresponsive and non-specific cells but no shift in ocular dominance. For normal ocular dominance to be maintained it appears to require input from both eyes. An increase in the proportion of cells with non-specific receptive fields following deprivation also implies that the maintenance of response properties of cells require normal visual input. It does not, however, suggest that visual experience is necessary to develop an adult-like visual system. The system instead may be mature at the time of birth. What is clear from deprivation studies is that certain features of the visual system can not be influenced by visual experience, as deprivation studies, using restricted viewing environments, are unable to re-shape the normal receptive field properties of cells thus resulting in a substantial increase in the number of non-responsive cells.

1.7 2-Deoxyglucose studies

The preceding discussion has focused primarily on electrophysiological studies aimed at determining the response properties of the kitten's visual system at the time of eye opening and how deprivation affects those response properties. Problems inherent in electrophysiological recording in young animals may have contributed to the lack of consensus concerning the level of maturity of the newborn's visual system. Slight alterations in the animal's physiological state during recording can be accompanied by changes in visual

cortical cell response properties which may lead researchers to report unresponsive or non-specific cortical cells, even in animals with normal visual experience (Blakemore & Van Sluyters, 1975). As Hubel and Wiesel (1963) demonstrated, cellular recording in the young kitten differs from recordings in adult animals in that cells in the kitten respond sluggishly to stimulation and show a greater tendency to fatigue. This, paired with the difficulties found in driving cells in deeply anaesthetized animals, makes it difficult to determine whether dissimilarities in the response properties of cells between the adult and newborn animal are related to differences in susceptibility to anaesthesia or whether they are attributable to divergence in the properties of the cortical cells. Testing of freely moving animals circumvents some of the problems created by anaesthesia. The 2-deoxyglucose technique allows researchers to examine the visual system in freely moving non-sedated animals.

The 2-deoxyglucose (2-DG) method takes advantage of the highly crossed guinea pig visual system. Occlusion of one eye during testing enables a single hemisphere to receive visual stimulation while the non-stimulated hemisphere serves as a control. Autoradiographic techniques assume a direct relationship between physiological changes in cerebral functioning and the rate of cerebral glucose metabolism (Sokoloff, 1977). The normal substrate of cerebral energy metabolism is oxygen and glucose. Use of 2-deoxy-D-[C^{14}]

glucose, a labelled analogue of glucose, allows researchers to measure the rate of energy metabolism in discrete regions of the brain. Once it has been introduced into the blood stream, 2-Deoxyglucose is transported bidirectionally across the blood-brain barrier by the same carrier that transports glucose (Sokoloff, 1984). Within the cerebral tissue it is phosphorylated by hexokinase, becoming 2-deoxyglucose-6-phosphate. 2-Deoxyglucose-6-phosphate, unlike glucose-6-phosphate, cannot be further converted into fructose-6-phosphate and is an unsuitable substrate for glucose-6-phosphate dehydrogenase. It remains, essentially trapped in the tissue, allowing measurement of the accumulating product, radioactivity labelled glucose-6-phosphate (Sokoloff, 1977). Figure 1 illustrates the theoretical model of 2-deoxyglucose utilization in the central nervous system (Sokoloff, 1991).

The rate of cerebral glucose metabolism can vary from structure to structure, although values in structures composed primarily of white matter are consistently lower than those of grey structures (Sokoloff, 1974). The average value in grey matter is 3 times that of white matter (Sokoloff, 1977).

Glucose utilization in the brain of a resting animal is associated with cellular processes which include cellular maintenance, protein synthesis and axoplasmic transport (Mata, Fink, Gainer, Smith, Davidson, Savaki, Schwartz and Sokoloff, 1980). Increases in energy metabolism, seen with visual stimulation, are thought to partially be a function of

2-Deoxyglucose Technique:

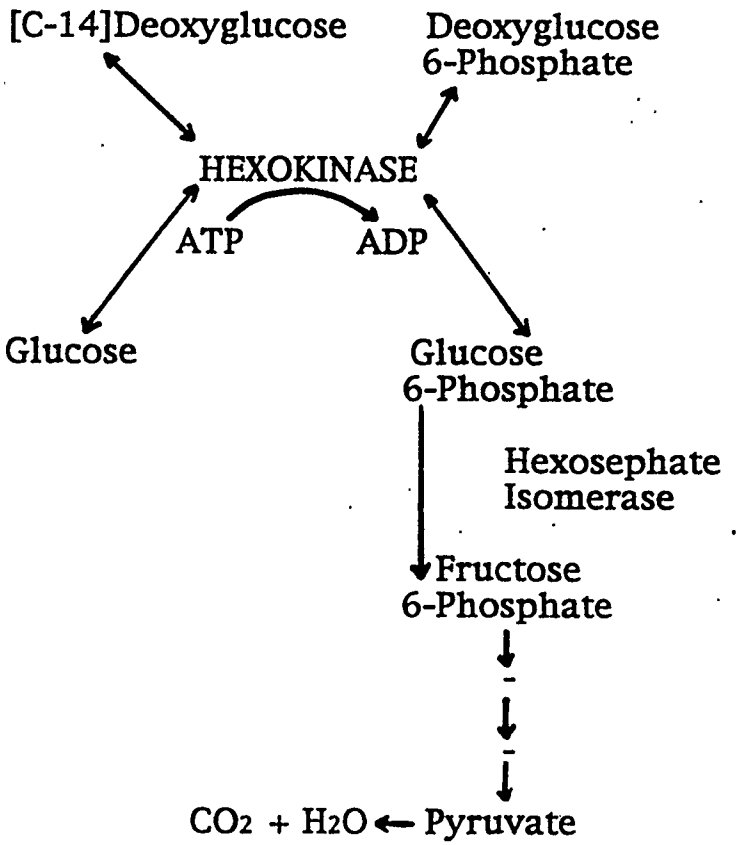


Figure 1.1. Theoretical model of 2-deoxyglucose utilization in the central nervous system (Sokoloff, 1991).

increased activity by the sodium pump (Sokoloff, 1977).

Most authors agree that patterned stimuli are maximally effective in driving visual cortical cells. Two-deoxyglucose studies confirm that a distinguishing feature of mature cortical neurons is that spatial patterns lead to an increase in metabolic activity whereas diffuse light does not. Using the 2-deoxyglucose technique, Rooney and Cooper (1988) exposed adult rats to striped stimuli resulting in elevated metabolic activity in the lateral geniculate nucleus, superior colliculus, lateral posterior nucleus and the visual cortex. Diffuse light stimulation, in contrast, served as a marginally effective stimulus for the lateral geniculate nucleus and strongly suppressed superior colliculus metabolic activity. No change in metabolic activity occurred in the visual cortex with diffuse illumination.

In a similar 2-DG study Gafka (1991) examined the metabolic properties of the rat visual system in both adult and visually inexperienced animals. On the 14th day postnatally, at the time of eye opening, cortical metabolic activity increased when the visually inexperienced animals were exposed to either patterned or diffuse light stimulation. This indicates that in the rat the metabolic response of cortical neurons to diffuse illumination is not mature at birth. Unlike visually inexperienced animals, the visual cortex of adult rats was unaltered by diffuse light stimulation.

Subcortically the pattern of metabolic activity found in the lateral geniculate nucleus of both adult and neonatal animals was the same regardless of whether they were tested with patterned or diffuse light. Patterned stimulation significantly heightened geniculate activity whereas diffuse stimulation only slightly increased activity.

In the superior colliculus diffuse light stimulation failed to suppress metabolic activity in visually inexperienced rats as it usually does in adults. Visually inexperienced rats instead showed increased metabolic activity in the superior colliculus in response to diffuse light.

Thus it appears that when adult and visually inexperienced rats exposed to diffuse or pattered light stimulation are compared the following differences emerge: Diffuse light is an effective stimulus for cortical cells of the visually inexperienced rat but not the normally reared adult rat. Diffuse light suppresses metabolic activity in the superior colliculus of the adult rat but does not alter activity in the infant. As with electrophysiological studies the dissimilarity in metabolic activity in adult and infant rats might suggest that visual experience is necessary for conferring adult status to the visual system, although maturation alone might be responsible for changes in receptive properties of visual cells.

The results of 2-DG analysis of the effects of monocular deprivation on the rat visual system are inconsistent with

electrophysiological studies. Cooper, Thurlow, Jeeva and Gafka (1992) found that metabolic activity was greater in the visual cortex, lateral geniculate and superior colliculus fed by the deprived eye as compared to the hemisphere fed by the non-deprived eye. Electrophysiological studies would predict decreased metabolic activity in the deprived hemisphere paralleling the increase in silent or non-responsive cells subsequent to deprivation. Similarly, Gafka (1991) binocularly or monocularly lid-sutured rats 2 days prior to the time of normal eye opening for a duration of 3 weeks. At this time animals were tested using either steady or flashing diffuse light. As expected deprived animals showed increased 2-DG uptake in response to diffuse light in the visual cortex and the lateral geniculate nucleus. Gafka was unable to replicate earlier findings of elevated glucose uptake in the superior colliculus. This may be due to disparities in the length of the deprivation period, 6 vs 3 weeks.

The authors argue that elevations of metabolic activity reflect a reduction in the receptive field specificity of cells. It is possible that deprivation, like dark rearing, maintains the visual system in an immature state, a time in which cortical neurons will respond to diffuse illumination with increased carbon-14 uptake.

1.8 Anatomy of the guinea pig visual system

Retina

Visual receptors in the retina of the guinea pig are

predominantly rods (Cooper & Schiller, 1975; Miles, Ratoosh & Meyer, 1956).

Lateral geniculate nucleus

The lateral geniculate is divided into larger dorsal and smaller ventral areas (Hess, 1955), both are devoid of obvious lamination (Vaidya, 1963). The majority of the retinogeniculate input is crossed. It is estimated that chiasmal decussation of the optic nerve of the guinea pig is 95-99% complete, leaving only a small number of ipsilateral projections to the geniculate (Creel & Goilli, 1972). The dorsal lateral geniculate nucleus (LGNd) of the guinea pig is subdivided into two sectors, alpha and beta, as in the rabbit (Giolli & Creel, 1973). The beta sector forms the rostromedial segment of the geniculate. The remaining segment comprises the alpha sector. The dorsomedial region of the dorsal lateral geniculate receives ipsilateral input intermixed with sparse contralateral input. The alpha sector of the LGNd receives a large contralateral retinal input (Creel & Giolli, 1972). In the ventral lateral geniculate nucleus (LGNv) contralateral projections are dense throughout with the exception of the dorsomedial portion which receives input from the ipsilateral retina (Giolli & Creel,1973).

Superior Colliculus

Fibres of the medial division of the optic tract and the superior quadrigeminal brachium enter the stratum opticum of the superior colliculus terminating in the stratum zonale,

stratum griseum superficial and stratum opticum (Giolli & Creel, 1973; Hess, 1958). Contralateral projections are greatest to the stratum griseum superficial and sparsest to the stratum zonale. The stratum opticum receives a moderate number of projections from the contralateral eye. A small region of the rostrolateral portion of the colliculus receives ipsilateral projections, this region corresponds to the inner portion of the stratum griseum superficial (Giolli & Creel, 1973).

Visual Cortex

Visual cortex in the guinea pig occupies a large portion of occipital cortex. Area 17 lies between the fissura sagittalis lateralis and the lateral groove, extending approximately 6mm rostrally from the occipital pole (Spatz, Vogt, & Illing, 1991) (See Figure 2.2). The visual cortex receives direct projections from the lateral geniculate nucleus and indirect projections from the superior colliculus (Spatz et al., 1991).

1.9 Development of the hypothesis

Understanding the relative contribution of heredity and the environment to the formation of a mature visual system would greatly enhance our knowledge of the developmental processes. Demonstrations of adult-like receptive field properties in cells of visually inexperienced animals support the essential contribution of genetic factors in the development of vision. Despite the significance of these

findings some researchers have suggested that visual experience is the crucial factor in establishing a mature visual system. Unfortunately, deprivation studies have not resolved the disagreement about the degree of stimulus specificity that can be found in the visual cells of an animal that has never experienced a normal visual environment. Numerous reasons can be given as to why researchers have reported such contradictory findings, the most compelling reason being the immaturity of the animals tested. Newborn and young animals are highly susceptible to the effects of anaesthesia, the level of anaesthesia produced with the same dose of anesthetic can often vary within a single animal. Even in adult animals high doses of anaesthesia can result in non-responsive cortical cells (Hubel & Wiesel, 1963). Interestingly, cells recorded from the striate cortex of the anaesthetized newborn rhesus monkey do not respond more slowly or fatigue as quickly as in the newborn kitten (Wiesel & Hubel, 1974).

The rhesus monkey, unlike the cat, is a precocial species. The precocial mammal is characterized by strong musculature and a large well developed brain, with early growth rates of brain and muscle correlated with high levels of nutrition and maternal effort during gestation (Grand, 1992). The guinea pig, a precocial species, is considered to belong to the order Rodentia but is more developed at birth than other members of this order. The main period of

maturation occurs in-utero, during foetal development. The many sensory systems of the guinea pig, therefore, develop under different conditions of sensory input than in the altricial animal (Huang, Wyse, & Spira, 1990; Sedlacek, 1971). Evidence suggests that visual development in the guinea pig may conform to the same time table as in the altricial mammal although it occurs in the absence of visual stimulation (Langford & Sefton, 1992).

Fry (1983) compared the structure of the retina of precocial guinea pigs reared in the dark to animals reared in normal conditions to determine if visual deprivation during the postnatal period affected the morphology of the retina as it did in altricial species. Dark-rearing in the altricial rat and mouse results in increased formation of retinal synapses. Visual deprivation during the postnatal period did not modify the morphology of the guinea pig retina. The lack of effect was explained by the presence of critical period of net synaptic addition which occurred in the guinea pig before birth. Similarly, the formation of dendritic spines in the cerebral cortex of the guinea pig is neither triggered nor accelerated by an increase in environmental stimulation postnatally, the density of cortical synapses being the same in adult and newborn pigs (Schuz, 1986).

Additional evidence of the maturity of the guinea pig at birth comes from Huang et al. (1990) who recorded the mass electrical activity of the retina of cesarian delivered fetal

and neonatal guinea pigs in response to light stimulation. At 64 days a mature electroretinograph was found in the cesarian delivered fetal guinea pig, although the animal had no history of light exposure.

The present experiment was designed to make use of the precocial nature of the guinea pig and the 2-deoxyglucose technique in an attempt to gain better understanding of the role of genetic and environmental factors on the development of the visual system. Adult guinea pigs were compared to 1 day and 13 day old pigs lacking visual experience to determine if they showed a similar pattern of metabolic activity in response to striped and diffuse stimuli. Use of the 2-deoxyglucose technique allows testing of freely moving non-anaesthetized animals circumventing some of the problems of more invasive techniques.

Comparison of the metabolic response of visual neurons in adult and neonatal precocial guinea pigs exposed to spatial patterns and diffuse illumination could indicate the level of maturity present in the newborn guinea pig visual system. Previous 2-deoxyglucose research has demonstrated increased carbon-14 uptake in the mature rat cortex to patterned stimuli while diffuse illumination has no effect (Rooney & Cooper, 1988). The neonatal rat cortex, on the other hand, shows increased cortical activity to both spatial patterns and diffuse illumination (Gafka, 1991). Subcortically, the superior colliculus of the adult rat shows depressed metabolic

activity in response to diffuse light while the visually inexperienced rat shows an elevation in metabolic activity in the colliculus (Gafka, 1991).

Should the guinea pig visual system respond with a similar pattern of metabolic activity to spatial patterns and diffuse light adult animals would be expected to show no change in metabolic activity in the visual cortex and suppression in the superior colliculus. Additionally, if genetic factors were largely responsible for visual system development the neonatal guinea pig would be expected to show a pattern of 2-deoxyglucose uptake that is similar to the adult. Conversely, the pattern of uptake in the newborn would be expected to vary from the adult if environmental stimulation conferred the response properties of the mature visual system. Dark reared, thirteen day old animals, were also tested to assess visual system responding in more mature but visually inexperienced animals.

CHAPTER 2

2.1 Method

Subjects

Forty-eight pigmented English Short Hair guinea pigs (Cavia porcellus) served as subjects. The animals were obtained directly from Oak Hills Ranch, Quebec or bred at the University of Calgary from parent stock. Sixteen subjects were tested in each of the following age groups: one day postnatal, thirteen days postnatal and adult. Four animals of each age

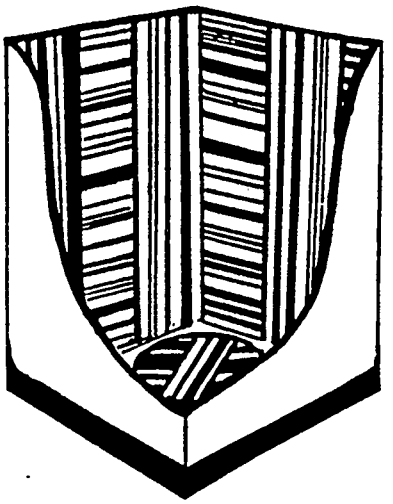
were tested in each of the 4 test conditions. Guinea pigs were considered adult when they had reached sexual maturity at approximately 3 months of age and weighed about 525 grams. One day and thirteen day old guinea pigs were born and remained in complete darkness until the time of testing. Adult animals were housed under a 12 hour light/dark schedule with food and water available ad lib.

Test apparatus

The two visual stimulation chambers, striped or diffuse (see Figure 2.1) and two illumination conditions, flashing or steady were used in combination to produce four test conditions: flashing diffuse (FD), flashing stripes (FS), steady stripes (SS) and steady diffuse (SD). The inner surface of the striped chamber was covered with a pattern of alternating black and white stripes. This 28 x 28 x 38 cm high Lucite chamber was rotated around the guinea pigs at 1.5 revolutions per minute in both clockwise and counterclockwise directions for 15 second periods interspersed with 6 second periods of immobility. The diffuse chamber, a 30 x 30 x 38 cm high white plexiglass box, remained immobile throughout the 45 minute test period.

Flashing light was presented in 8 μsec flashes at 5 Hz using a Grass Photostimulator-2 with the lamp centred 40 cm above the chamber. Steady light was presented to the walls and ceiling of the striped chamber using five 60 watt incandescent bulbs so that the brightness of the white stripes were 330

A) STRIPED CHAMBER



B) DIFFUSE CHAMBER

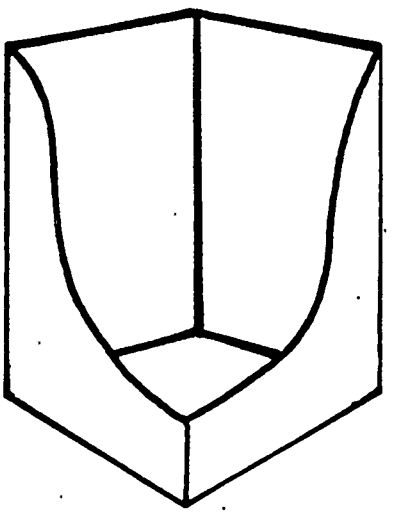


Figure 2.1. Test chambers. (1) Striped (2) Diffuse

cd/m^2 and the black stripes were 61 cd/m^2 as determined by a Salford Electrical Instrument photometer. The walls and lid of the diffuse chamber were lit with ten, 150-watt incandescent bulbs, two at each face of the chamber. No other source of illumination was present during the test conditions.

Exposure to the test apparatus was controlled through the use of headgear modelled to fit the guinea pigs and to selectively restrict vision to one eye. A black occluder attached to side of the headgear blocked all light from entering the eye. The hemisphere contralateral to the occluded eye therefore recieved relatively little visual stimulation during testing.

Surgery

Two days prior to testing the adult guinea pigs were anaesthetized using a combination of Ketamine (4.25 mg/kg) and Xylazine (0.75 mg/kg). Atropine Sulfate (5 mg/kg) was given 30 minutes before the anesthetic. The left jugular vein was cannulated with Dow Corning Silastic tubing (0.119 cm outside diameter) filled with heparin solution. The tubing was plugged and fed subcutaneously to between the shoulder blades, where it was secured with thread to wound clips and kept in a pocket formed underneath the skin. A Teflon post, cemented to the skull using Vet Bond and dental cement, was used to secure headgear which restricted visual stimulation to a single eye during the test period. No surgery was performed on the newborn and 13 day old guinea pigs, the headgear was instead

"rubber cemented" directly onto the fur at the top of the head (Gafka, 1991). Care was taken not to irritate the animals' eyes with the adhesive.

2-Deoxyglucose injection

Prior to injection of 2-deoxyglucose (2-DG) one eye was occluded with a black plastic lens fitted on to the headgear, which blocked all light from entering the eye. The alternate eye remained uncovered in striped test conditions or covered with a white plastic lens, which served to diffuse incoming light, in the diffuse test conditions. The headgear was secured to the Teflon post in adult animals. Infants and 13 day old animals had the headgear attached directly to the head with rubber cement and were given a 30 minute adaptation period prior to testing. In the adult guinea pig the catheter tubing was released by cutting the thread that secured it to the wound clips. The animal was then injected, via the catheter, with 2-DG (American Radiolabeled Chemicals 2-deoxyglucose in saline carrier, dose 100 μCi/kg), followed by an equivalent amount of saline solution to flush the catheter tubing of radioactively labelled glucose. One and thirteen day old animals received intraperitoneal injections of 2-DG with a 3/8 inch 26 gage needle at a dose of 170 μCi/kg. The dose was adjusted to compensate for differences in the rate of glucose metabolism within adult and newborn animals (Gafka, 1991). After injection, guinea pigs were placed in the test chamber for 45 minutes to allow for uptake and clearance of

the 2-DG in accordance with the Sokoloff protocol (Sokoloff, 1984).

Histology and autoradography

Following the 45-min test period the guinea pigs were injected, via the catheter in adult animals and i.p. in one and thirteen day animals, with a deeply anaesthetizing dose of sodium pentobarbital. Adult guinea pigs were perfused through the left ventricle with 60 ml of saline followed by 120 ml of modified Hand's solution (Hand, 1981). Infant and thirteen day old guinea pigs were perfused with 40 ml of saline and 80 ml of modified Hand's solution. The brain was removed, bathed in Lipshaw embedding matrix, frozen in 2-methyl butane (-60 °C) and mounted on a metal pedestal with Tissue Tek O.C.T. (Fisher Scientific). The brain was sectioned in a cryostat (American Optical, Cryo-Cut II) and the 30 μm sections mounted on heated slides. Every 20th section from the first 300 sections was saved. From section 301 onward every section was saved. The mounted brain sections were exposed to Du Pont Microvision mammography film along with seven Amersham (C^{14}) methylacrylate standards for 14 days before being developed. The film was developed using Kodak Industrex Manual developer for 90 seconds. It was then bathed in stop for 30 seconds, fixer for 4 minutes, left under running water to remove any chemicals and dipped in Kodak Photo-Flo 200 and allowed to dry.

Autoradiograph analysis

A microcomputer imaging device (MCID) was used to provide a relative Carbon-14 measure of 2-deoxyglucose uptake in the guinea pig brain. The autoradiographs were placed on an illumination box and the amount of light transmitted through the autoradiographs was measured using a COHU camera and Micro-Nikkor lens.

The MCID system was used to convert the light density readings from the ARGs to relative optical density units (RODs). There are several steps in this process. In the first step, light transmitted through the ARGs induces a voltage in a light sensor in the camera, which is then digitized. These digitized values are then displayed on the computer as gray-scale values. Since these gray-values are dependent upon the illumination they are converted to relative optical density values (RODs). Rod values are then calibrated to allow the reading of regional density values as carbon-14 values. This was accomplished by using a set of standards of known carbon-14 activity called Amersham standards which are placed along with the brain sections during exposure to the mammography film.

Light density readings were taken for each standard and interpolation was used to calculate the density values which lay between the seven Amersham standard values. Density values measured from visual structures could then be converted into the corresponding carbon-14 values by comparing them to the

relative optical density function created with the standards.

To decrease the degree of variation between density readings and improve comparability among subjects the relative C-14 ratio values were normalized by dividing them by the average C-14 ratio value from control brain sections. Density values for a single visual structure were taken from each hemisphere. The average density value from the non-stimulated hemisphere of the brain, which recieved projections from the occluded eye, was subtracted from the average density value from the stimulated hemisphere to obtain a mean hemisphere differences score for each visual structure. Values for each hemisphere were compared to determine whether there was greater metabolic activity in the hemisphere fed primarily by the stimulated eye compared to the hemisphere fed primarily by the non-stimulated eye.

Three density readings were taken from each of the following regions in 6 separate brain sections: ventral lateral geniculate nucleus and monocular and binocular dorsal lateral geniculate nucleus. The six density reading obtained from the mnLGN and biLGN were combined during statistical analysis. Eight brain sections were sampled for the superior colliculus, with 6 density readings taken from each of the superficial layers, SGS, SO and SGM (see Figure 2.2). In the striate cortex eighteen separate brain sections were sampled. As the visual cortex extends 6 mm rostrally from the occipital pole six brain sections were sampled from the anterior, medial

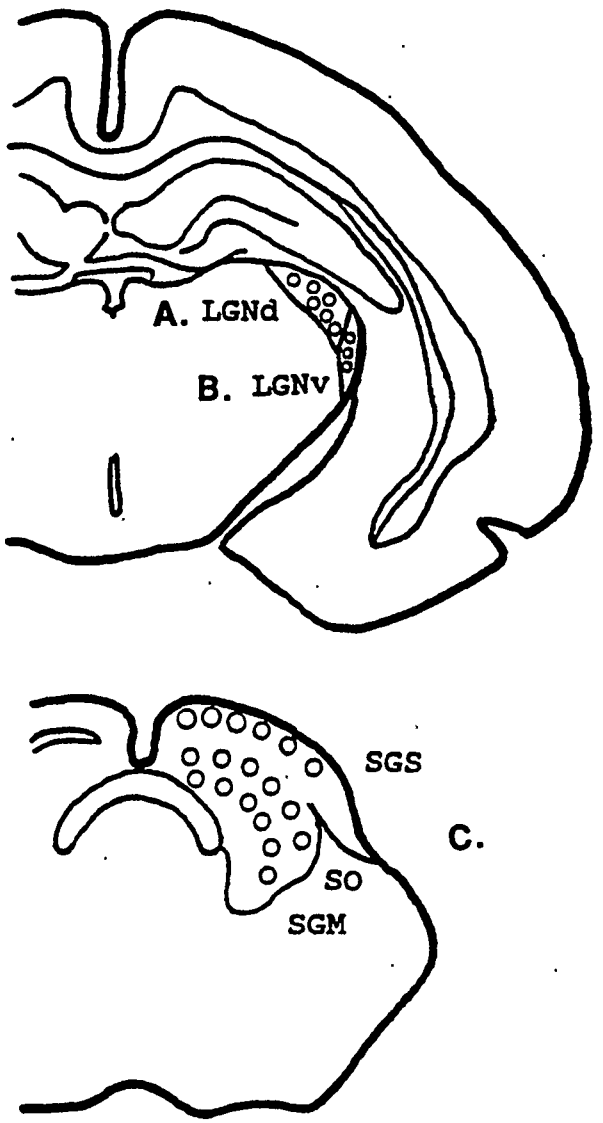


Figure 2.2. Sample locations for LGN and SC. The sample locations for density readings taken in the (A) monocular (mnLGNd) and binocular (biLGNd) dorsal lateral geniculate nucleus (B) ventral lateral geniculate nucleus (LGNv) (C) superior colliculus. Three layers of the colliculus were sampled, the stratum griseum superficiale (SGS), stratum opticum (SO), and the stratum griseum mediale (SGM).

and posterior portion of area 17. The areas sampled are labelled Region A (anterior), Region B (medial) and Region C (posterior) in all figures. Twenty-four density readings were taken from each brain section, 12 from the stimulated hemisphere and 12 from the non-stimulated hemisphere (see Figure 2.3). The density readings from Region A, Region B and Region C of the stimulated hemisphere and Region A, Region B and Region C of the non-stimulated hemisphere were combined for statistical analysis.

2.2 Results

A similar pattern of metabolic activity was found in adult, 1 day and 13 day old guinea pigs in response to Flashing Stripes, Flashing Diffuse, Steady Stripes, and Steady Diffuse test conditions. Flashing stripes led to greater 2-deoxyglucose uptake in the stimulated as compared to non-stimulated hemisphere in cortex and sub-cortical visual structures than steady stripes, flashing diffuse or steady diffuse. Steady diffuse illumination did not activate the cortex and depressed activity in the superior colliculus.

Cortex

A two way analysis of variance (ANOVA) using test condition and age as the independent variables and mean hemisphere difference scores as the dependent variable indicate that the metabolic response in the cortex did not significantly differ among age groups ($p>.05$). In addition a non-significant age by test condition was found ($p>.05$).

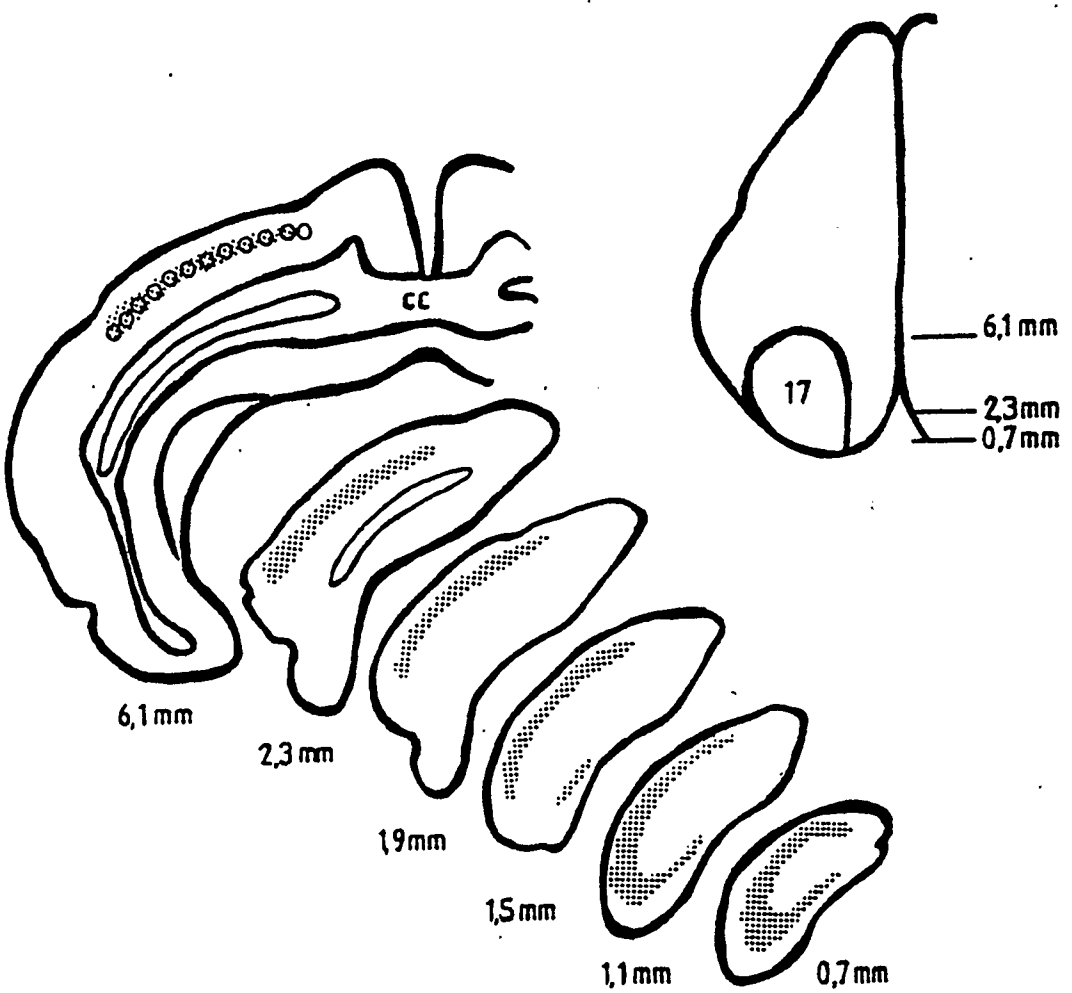


Figure 2.3. The sample locations for density readings taken in visual cortex.

Figure 2.4 illustrates the results for the adult, 13 day and 1 day old guinea pigs exposed to flashing stripe or flashing diffuse test conditions. All age groups showed greater carbon-14 uptake in the stimulated hemisphere than non-stimulated hemisphere in area 17 when exposed to the flashing stripe (FS) test condition. Flashing diffuse (FD) test conditions, as expected, did not elevate cortical metabolic activity. Figure 2.5 shows the mean hemisphere difference scores in area 17 of guinea pigs exposed to steady stripes (SS) and steady diffuse (SD) experimental conditions. In the flashing stripes, flashing diffuse, steady stripes and steady diffuse test conditions the mean hemisphere difference scores do not vary across the three sampling regions of the cortex: Region A, Region B and Region C. The three cortical regions were combined during statistical analysis.

A significant difference in metabolic activity was found with the two-way ANOVA between the stimulus conditions ($F_{3,36}$=25.872, p<.0001). One way ANOVA's performed across stimulus conditions, when scores for all age groups were combined, show greater uptake to FS than to FD ($F_{1,22}$=32.536, p<.0001), to FS than to SD ($F_{1,22}$=40.768, p<.0001), to SS than to FD ($F_{1,22}$=25.583, p<.0001) and to SS than to SD ($F_{1,22}$=32.936, p<.0001). In descending order the mean hemisphere difference scores for each stimulus condition across all visual centres are presented in Table 2.1. From Table 2.1 it can be seen that the visual cortex responds best

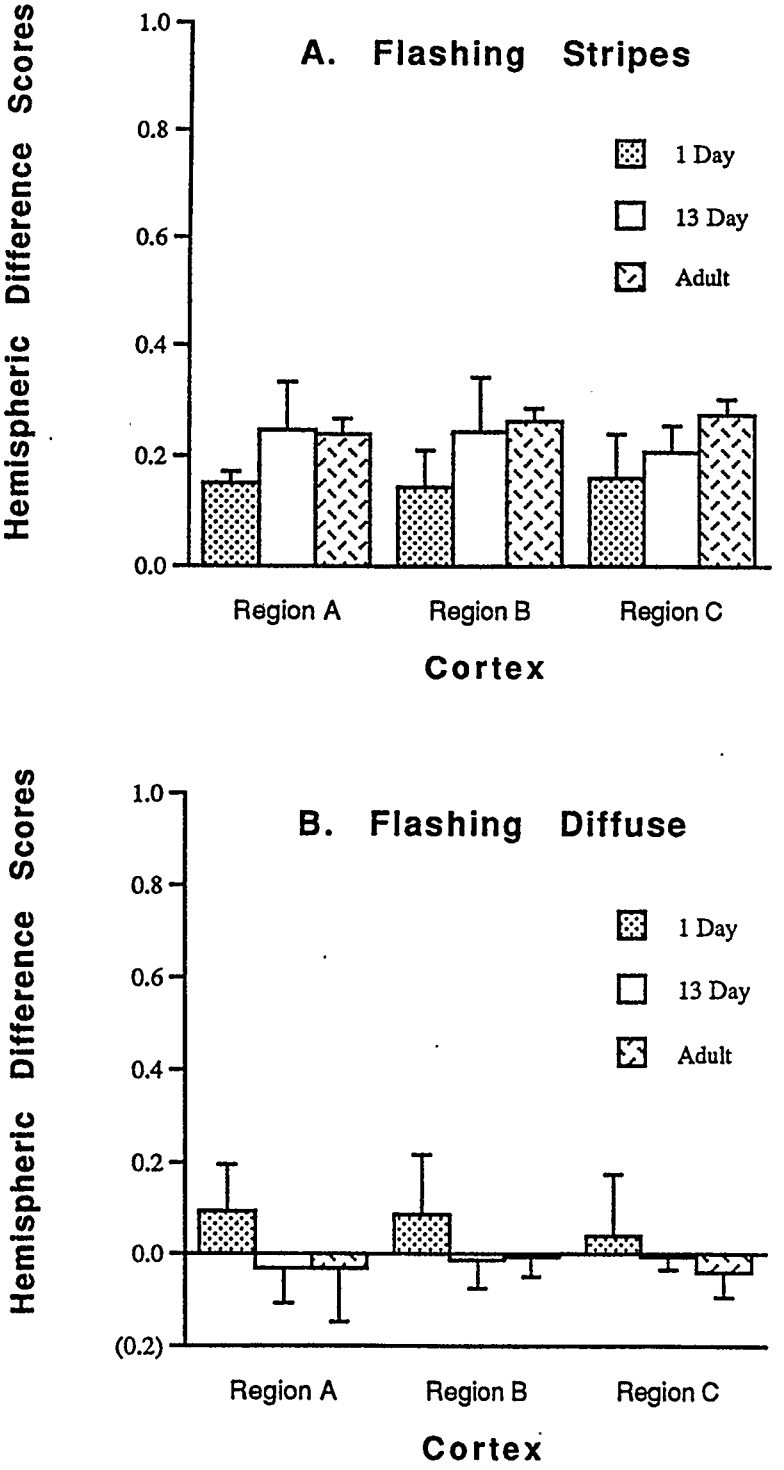


Figure 2.4. Cortical hemispheric difference scores for FS and FD. Mean hemispheric difference scores for cortex of 1 day, 13 day, and adult guinea pigs exposed to flashing striped (A) and diffuse (B) test conditions. Error bars in all figures represent standard error of the mean.

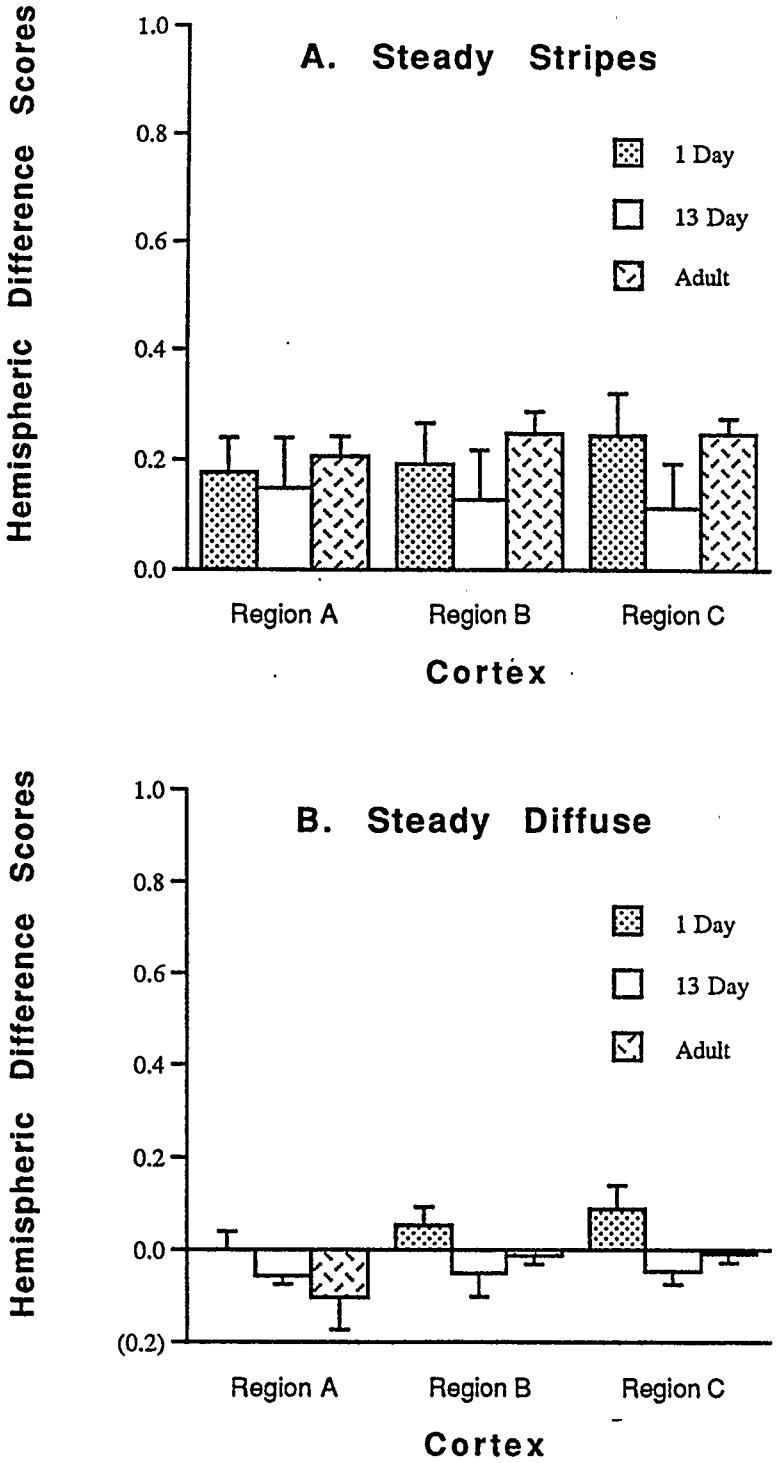


Figure 2.5. Cortical hemispheric difference scores for SS and SD. Mean hemispheric difference scores for cortex of 1 day, 13 day, and adult guinea pigs exposed to steady striped (4-60 watt) (A) and diffuse (10-150 watt) (B) test conditions.

Visual Structure	Strongest Effect.....Weakest Effect			
Cortex	FS $\overline{x}$=0.21	SS $\overline{x}$=0.19	FD $\overline{x}$=0.01	SD $\overline{x}$=-0.02
LGNd	FS $\overline{x}$=0.57	SS $\overline{x}$=0.46	FD $\overline{x}$=0.42	SD $\overline{x}$=0.18
LGNv	SS $\overline{x}$=0.46	FS $\overline{x}$=0.35	SD $\overline{x}$=0.26	FD $\overline{x}$=0.24
SGS	FS $\overline{x}$=0.53	SS $\overline{x}$=0.36	FD $\overline{x}$=0.34	SD $\overline{x}$=-0.04
SO	FS $\overline{x}$=0.35	SS $\overline{x}$=0.18	FD $\overline{x}$=0.13	SD $\overline{x}$=0.00
SGM	FS $\overline{x}$=0.15	SS $\overline{x}$=0.06	FD $\overline{x}$=0.04	SD $\overline{x}$=0.01

Table 2.1. One-way ANOVAs comparing stimulus condition. In ascending order, for all three age groups combined, mean hemispheric difference scores in each test condition for the cortex, dorsal lateral geniculate nucleus, ventral lateral geniculate nucleus, stratum griesum superficial, and stratum opticum combined with stratum mediale.

to striped stimuli. Flashing diffuse light and steady diffuse light do not appear to be effective stimuli for cortical neurons as these conditions did not significantly elevate or diminish metabolic activity of the stimulated hemisphere over that of the control hemisphere.

Dorsal lateral geniculate nucleus

Statistical analysis using 2-way ANOVA revealed that there were no significant age differences ($p>.05$) and no significant age by test condition interaction ($p>.05$). The scores for the monocular and binocular region of the dorsal lateral geniculate nucleus were combined into a single region, LGNd, for analysis. Figure 2.6 shows that mean hemisphere difference scores for FS and FD were similar in the monocular and binocular dorsal lateral geniculate nucleus of adult, 13 day, and 1 day old pigs. The mean hemisphere difference scores for animals in the steady diffuse and steady stripes test conditions are depicted in Figure 2.7.

A two way analysis of variance (ANOVA) using test condition and age as the independent variables and mean hemisphere difference scores as the dependent variable indicate that the metabolic response in the dorsal lateral geniculate nucleus differed significantly between stimulus conditions ($F_{3,36}=8.228$, $p<.0001$). Planned comparisons showed that the striped conditions always led to greater metabolic activity than the diffuse light conditions; FS compared to SD ($F_{1,22}=21.631$, $p<.0001$), SS compared to SD ($F_{1,22}=11.377$,

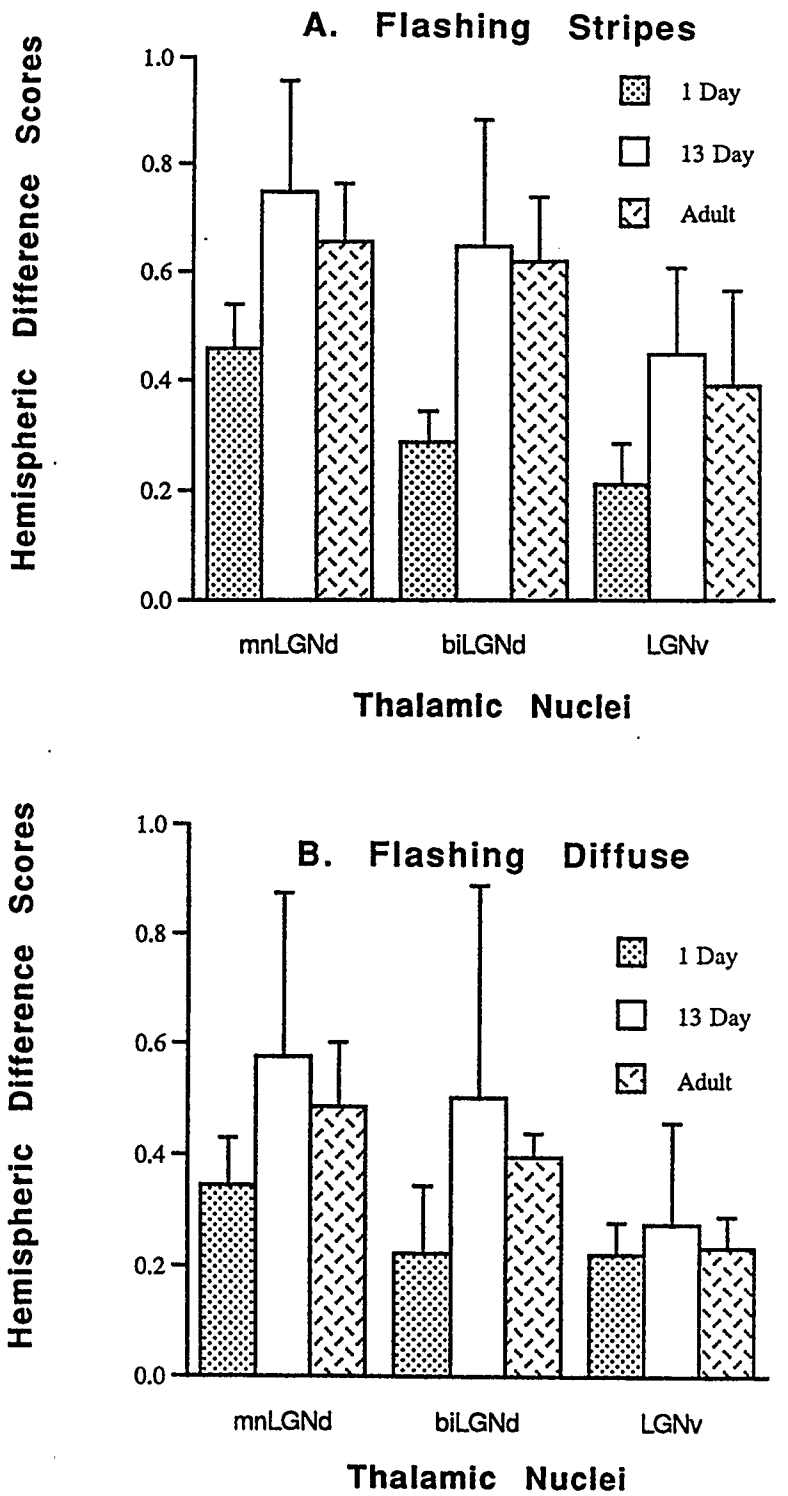


Figure 2.6. Thalamic hemispheric difference scores for FS and FD. Mean hemispheric difference scores for thalamus of 1 day, 13 day, and adult guinea pigs exposed to flashing stripes (A) and diffuse (B) test conditions.

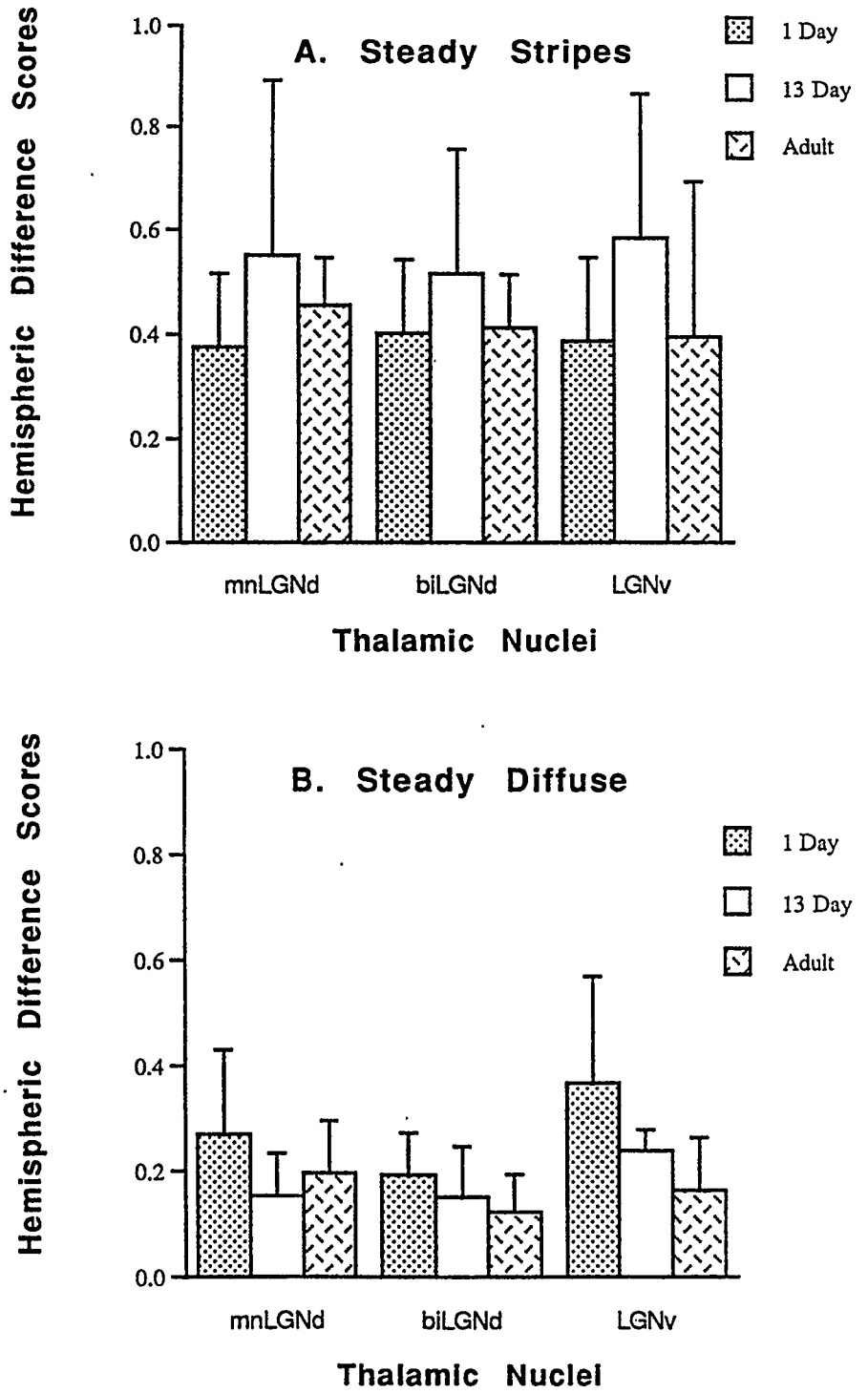


Figure 2.7. Thalamic hemispheric difference scores for SS and SD. Mean hemispheric difference scores for thalamus of 1 day, 13 day, and adult guinea pigs exposed to flashing striped (4-60 watt) (A) and diffuse (10-150 watt) (B) test conditions.

$p<.002$). When flashing and steady diffuse light are compared, flashing diffuse increased metabolic activity more than steady diffuse in the LGNd; FD compared to SD ($F_{1,22}=8.341$, $p<.006$).

Table 2.1 shows that mean hemisphere difference scores were largest in the FS test condition across all age groups, moderate in the SS and FD test conditions, and the smallest in the SD condition. As previously found in cortex, striped stimuli were the most effective in elevating metabolic activity in the geniculate. However, while diffuse light conditions are poor stimuli for area 17 they are more effective in elevating metabolic activity in LGNd.

Ventral lateral geniculate nucleus

The mean hemisphere scores for the ventral lateral geniculate nucleus of adult, 13 day and infant animals across all four stimulus conditions are depicted in Figures 2.6 and 2.7. There was no significant difference in metabolic activity between the age groups ($p>.05$). A non-significant age by test condition was also found ($p>.05$).

The metabolic response in the ventral lateral geniculate nucleus differed significantly between stimulus conditions as shown by a two way analysis of variance (ANOVA) using test condition and age as the independent variables and mean hemisphere difference scores as the dependent variable ($F_{3,36}=3.280$, $p<.032$). There were significantly larger mean hemisphere difference scores for animals exposed to SS compared with FD ($F_{1,22}=7.530$, $p<.009$). A significantly

greater difference was also found for SS compared to SD ($F_{1,22}$=6.605, p<.014). Examination of the group means (Figure 2.1) reveals that striped stimuli produced greater carbon-14 uptake in the stimulated hemisphere over that of the control hemisphere in the ventral lateral geniculate nucleus.

Superior Colliculus

Figures 2.8 and 2.9 show the SGS, SO, and SGM mean hemisphere difference scores for all four test conditions. The superior colliculus of adult, 13 day old and 1 day old guinea pigs demonstrated increased metabolic activity in response to flashing stripes, steady stripes and flashing diffuse conditions. Exposure to steady diffuse light resulted in depressed of SGS metabolic activity in the adult and 13 day animals.

An independent two-way analysis of variance (ANOVAs) conducted for each region of the superior colliculus, SGS, SO, and SGM, using test condition and age as the independent variables and mean hemisphere difference scores as the dependent variable indicate that the metabolic response in the SGS, SO and SGM did not significantly differ between age groups (p>.05). Non-significant age by test condition interactions were found for the SGS, SO, and SGM in each of the three ANOVA's (p>.05).

Stratum griseum superficiale (SGS)

A two way analysis of variance (ANOVA) using test condition and age as the independent variables and mean

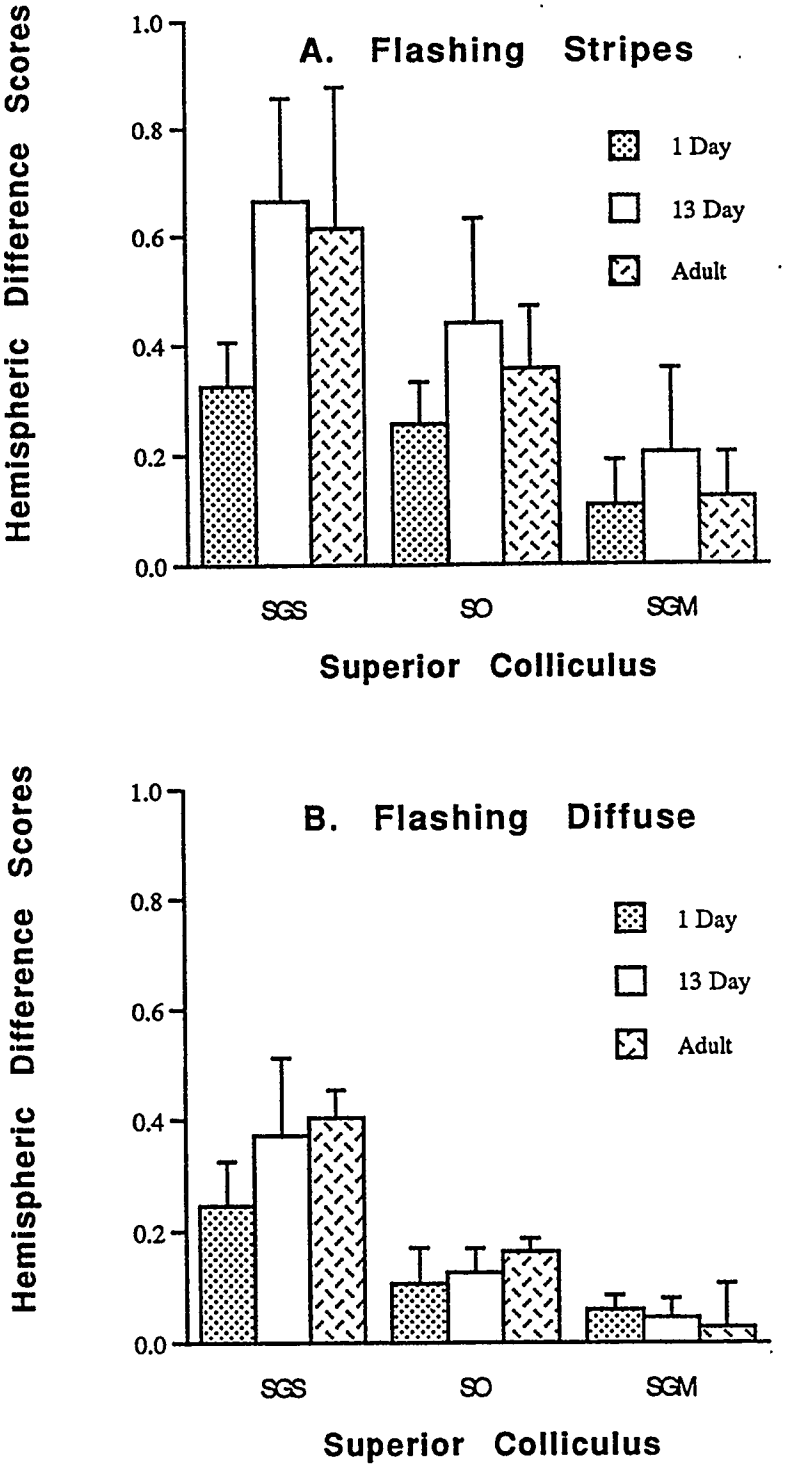


Figure 2.8. Colliculus hemispheric difference scores for FS and FD. Mean hemispheric difference scores for superior colliculus of 1 day, 13 day, and adult guinea pigs exposed to flashing striped (A) and diffuse (B) test conditions.

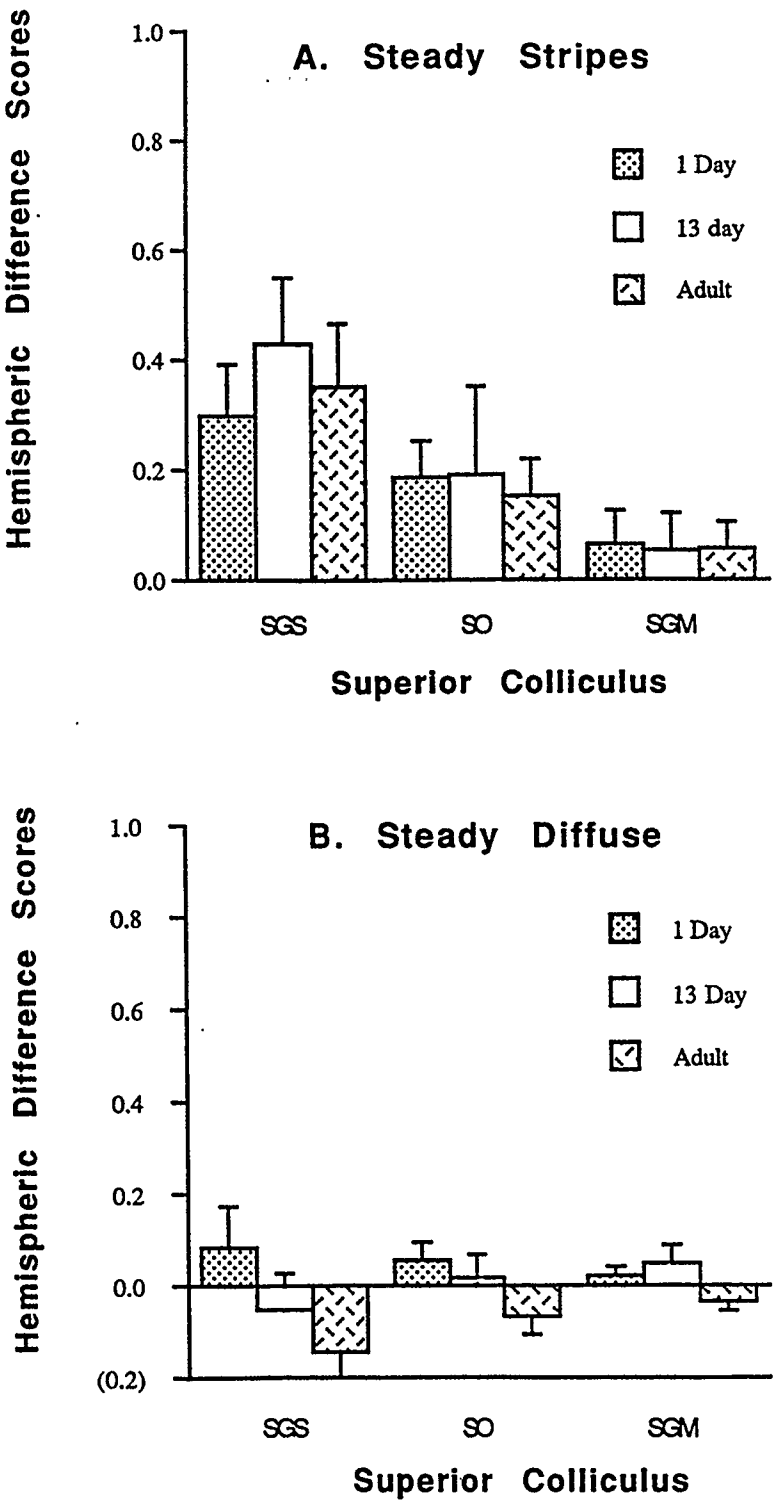


Figure 2.9. Colliculus hemispheric difference scores for SS and SD. Mean hemispheric difference scores for superior colliculus of 1 day, 13 day, and adult guinea pigs exposed to flashing striped (4-60 watt) (A) and diffuse (10-150 watt) (B) test conditions.

difference scores as the dependent variable indicated a non-significant age and age by test condition interaction ($p>.05$) while the metabolic response in the SGS differed significantly between stimulus conditions ($F_{3,36}=19.215$, $p<.0001$). Planned comparisons made between stimulus conditions showed significantly greater metabolic activity in response to FS compared to all stimulus conditions; FS verses SS ($F_{1,22}=4.592$, $p<.038$), FS verses FD ($F_{1,22}=5.669$, $p<.022$), and FS verses SD ($F_{1,22}=48.874$, $p<.0001$). An equally significant difference was found for FD compared to SD ($F_{1,22}=21.252$, $p<.0001$) and for SS compared to SD ($F_{1,22}=23.503$, $p<.0001$). As with the cortex and the dorsal lateral geniculate nucleus, the striped test chamber paired with flashing light produced the greatest mean hemispheric difference scores in the stratum griseum superficiale (see Table 2.1).

Stratum opticum (SO)

The results were similar to those found in SGS, with a non-significant age and age by test condition interaction ($p>.05$) and the greatest mean hemispheric difference scores found in response to flashing stripes (Table 2.1). Mean hemisphere difference scores differed significantly between stimulus conditions ($F_{3,36}=14.061$, $p<.0001$). Flashing stripes produced significantly greater 2-deoxyglucose uptake in layer SO compared to all other stimulus conditions; FS compared to SS ($F_{1,22}=10.883$, $p<.002$), FS compared to FD ($F_{1,22}=16.974$, $p<.0001$), and FS compared to SD ($F_{1,22}=42.929$, $p<.0001$). In

addition, a significant difference in mean hemispheric difference scores was found when metabolic activity in response to steady stripes was compared to metabolic activity in response to steady diffuse ($F_{1,22}$=10.576, p<.002). As with the SGM, steady stripes and flashing stripes produced greater metabolic activity in the stimulated hemisphere than in the control hemisphere.

Stratum griseum mediale (SGM)

A two-way ANOVA revealed a non-significant age and age by test condition interaction (p>.05) and a significant main effect of test condition ($F_{1,22}$=3.879, p<.017). The greatest mean hemispheric difference scores were found in response to flashing stripes (Figure 2.1). Flashing stripes produced significantly greater 2-DG uptake in the SGM than all other stimulus conditions; FS compared to SS ($F_{1,22}$=5.058, p<.030), FS compared to FD ($F_{1,22}$=6.786, p<.012), and FS compared to SD ($F_{1,22}$=11.772, p<.001).

CHAPTER 3

3.1 Discussion

Previous 2-deoxyglucose work with the rat has shown that the metabolic activity of cortical area 17 in response to patterned and diffuse visual stimuli is indicative of the level of visual system maturity. Cortical neurons of the mature animal show no 2-DG uptake if stimulated by diffuse illumination, whereas, the immature cortex with its poorly defined neuronal receptive fields will show metabolic activity

when presented with diffuse illumination (Cooper, Thurlow & Jeeva, 1991; Gafka, 1991). Uptake of 2-DG in visual cortex in response to spatial patterns, however, is significantly elevated in both the adult and neonate (Rooney & Cooper, 1987; Gafka, 1991).

The present results show that in the cortex, striped stimuli elevated the metabolic activity of neurons while diffuse light had little or no effect on glucose metabolism of 1 day, 13 day and adult guinea pigs. This suggests that the metabolic response of the neonate guinea pig visual cortex to spatial patterns and diffuse illumination is mature at birth and, as in the case of the adult, is concerned with processing information about spatially arrayed light rather than diffuse light.

In subcortical nuclei of 1 day, 13 day and adult guinea pigs flashing stripes, steady stripes and flashing diffuse light were all effective in elevating carbon-14 uptake. In fact, unlike in the cortex, flashing diffuse light is no less effective than steady stripes in elevating thalamic or superior colliculus metabolic activity.

Paralleling metabolic activity in the adult rat, the adult and 13 day old guinea pigs showed suppressed stratum griseum superficiale (SGS) activity when exposed to steady diffuse light. Importantly, there was no significant age effect with respect to superior colliculus metabolic activity during exposure to steady diffuse illumination between adult,

13 day and 1 day old guinea pigs.

3.2 Conclusion

The purpose of this thesis was to determine whether the metabolic response properties of adult, and visually inexperienced 1 day and 13 day old precocial guinea pigs were similar. It was argued that a similar pattern of metabolic activity in the adult and visually inexperienced guinea pig would indicate that a mature metabolic response to spatial patterns and diffuse illumination is present at the time of birth and is able to develop in the absence of visual stimulation. In support of this position metabolic activity in response to striped and diffuse stimuli was similar in adult, 1 day and 13 day guinea pigs. A mature metabolic response to spatial patterns and diffuse illumination suggests that the receptive field properties of visual cells of the neonatal pig might also be mature at birth.

Hubel and Wiesel (1963) were the first to suggest that receptive fields of cells in the striate cortex of young, visually inexperienced kittens were the same as in adult cats. Cortical cells of kittens 8 to 20 days old strongly resembled cells of mature cats in their responses to patterned stimuli. Firing rates of neurons increased to slits of light, dark bars and edges, while steady diffuse illumination caused little or no change in firing rates. Nevertheless, Hubel and Wiesel acknowledged that the visual system displays plasticity and can be altered by a lack of exposure to spatially defined

light, as evidenced by monocular deprivation which results in deprived LGN cells being unable to drive cells in visual cortex. Control over visual cells is instead surrendered to LGN cells that are excited by the non-deprived eye, demonstrating that if parts of the visual system are not used they will atrophy or be taken over by functioning parts of the system.

Other studies which examined visually inexperienced animals at the time of eye opening contradicted the work of Hubel and Wiesel. These studies reported cells in the kitten that appeared to have non-specific receptive fields at the time of eye opening making it conceivable that experience with patterned light is instrumental in determining their eventual selectiveness.

Hubel and Wiesel have attributed the disagreement to difficulties in maintaining an adequate physiological state in neonatal animals during electrophysiological recording. Young animals are highly susceptible to entering into unphysiological states during anaesthesia. Previous work on the cat shows that it is often difficult to record from cells in deeply anaesthetized mature animals with normal visual experience. Given the neonates' unpredictable response to anaesthesia, then, it is difficult to determine whether dissimilarities in the response of visual cells of the adult and neonate are due to the anesthetic. While this argument can be made for electrophysiological work with immature animals it

is not applicable to the 2-deoxyglucose technique which tests animals in an unanesthetized, freely moving state.

Gafka (1991) used 2-deoxyglucose to examine the visual system of adult and visually inexperienced rats and found that in the rat, at least, some visual cortical cells are not functionally adult-like at the time of eye opening. At 14 days postnatal, the time of eye opening, an increase in 2-DG uptake was observed with diffuse illumination which did not disappear until day 35. In her experiment responsiveness to diffuse light would be difficult to attribute to an unphysiological state as the rats were unanesthetized during testing. Conceivably then, experience with spatially defined light may be necessary if visual cortical cells are to develop mature receptive field properties and respond only to spatially arrayed stimuli.

In keeping with this position Jeeva (1991) examined rats deprived 6 weeks from the time of normal eye opening and found visual cortical cells which responded to diffuse illumination. Monocular lid-suture, then, may arrest development of visual cortical cells in an immature state, indicating that visual experience normally plays a crucial role in establishing mature vision. However, this conclusion may not be warranted as it is possible that deprivation may not lead to a failure to form the neuronal connections essential for normal vision but rather to a disruption of predetermined connections during a critical period of maturation.

Should the environment be essential in the development of the rat visual system it would be expected that this would be also true for other rodents such as the guinea pig. In as much as the rat and guinea pig possess very similar visual systems it would be expected that the visual cortex of the neonatal guinea pig should be equally responsive to diffuse light. The neonatal guinea pig, however does not show significantly elevated cortical activity in response to diffuse light when compared to the adult as demonstrated in the present experiment. The visually inexperienced guinea pig, like the adult, only shows elevated 2-DG uptake in visual cortex when stimulated by spatially arrayed light. Apparently, visual experience is not necessary to make guinea pig visual system cortical cells responsive to light with spatial properties. Possibly the factor which differentiates the rat and the guinea pig is their level of cortical developmental maturity at birth.

The guinea pig is born very mature at birth and develops in utero for a longer time period than the rat. Thus at the day of eye opening the visual connections underlying mature vision have had a longer period to develop in the guinea pig. These findings suggest that the rat's responsiveness to diffuse light at the time of eye opening is attributable to immaturity rather than to a lack of visual experience. The rat visual system, then, is plastic at the time of eye opening but does not necessarily require visual experience to make cells

selectively responsive to light with spatial characteristics. The findings of this experiment indicate that at least for the guinea pig nature rather than nurture is responsible for the development of a mature visual cortex.

Although diffuse light was a poor stimulus for increasing 2-deoxyglucose uptake in the cortex of the guinea pig it is an effective stimulus subcortically especially under the flashing condition. Indeed, unlike in the cortex, flashing diffuse light is no less effective than steady stripes in elevating thalamic or superior colliculus metabolic activity. Comparable findings have been obtained for the adult rat by Cooper and Thurlow (1991) who reported that flashing diffuse and flashing pattern test conditions were equally effective in increasing uptake of radioactively labelled glucose in the lateral geniculate nucleus and superior colliculus.

Under the steady condition diffuse light is least effective subcortically in adult and 13 day old guinea pigs. Steady diffuse illumination marginally elevates thalamic activity in adult guinea and 13 day guinea pigs and, as in adult rats, suppresses colliculus activity below the level produced by darkness (Rooney & Cooper, 1988). It is possible that depressed metabolic activity indicates that the superior colliculus is responsible for monitoring change occurring in the visual environment (Macintosh & Cooper, 1989).

In one day animals, however, depression of superior colliculus activity is not found. Gafka (1991) reported a

similar trend in the SGS of rats with normal visual experience which were stimulated with steady diffuse light. At 14 days postnatal, SGS metabolic activity was elevated in the steady diffuse condition but by 21 days postnatal this elevation had disappeared and metabolic activity was now depressed. The lack of a significant age effect in the SGS of the guinea pig superior colliculus may be a reflection of the small sample size used in the present study or may instead indicate the need for a maturational period in which the genetically determined response properties of neurons are expressed. The data suggests that the latter is more probable since visually inexperienced 13 day guinea pigs exhibit depressed metabolic activity. Further work seems necessary to examine the phenomenon of depressed superior colliculus metabolic activity under steady diffuse illumination.

In conclusion, the present results make it clear that the functional properties of neurons which characterize the mature guinea pig visual system develop in the absence of visual experience. Neuronal connections required for mature metabolic activity in visual cells in response to spatial patterns and diffuse illumination must be present at the time of birth or shortly thereafter as all three age groups demonstrated a similar pattern of metabolic activity across all test conditions.

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