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Marina B. Roma
Pacific University

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Abstract

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MARINA B. ROMA

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Advisor:

Steven J. Cool, Ph.D.

The Role of Neural Inhibition
in the Development of Amblyopia

Author: Marina Roma
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Advisor:
Steven J. Cool, Ph.D

ABSTRACT:

One of the theories in the development of amblyopia is binocular inhibition. Support for this theory come from neurotransmitter studies. Dopamine is a modulatory neurotransmitter and may have a significant role in normal visual maturation and in the cortical plasticity during the critical period. This preliminary study assessed and compared, through autoradiographic techniques, the dopamine distribution in human fetal and neonatal visual cortex to adult primary visual cortex. The results shows a laminar and ontogenic distribution of dopamine receptor binding sites in adult and child visual cortex,with binding most distinct in layer IVc. The results suggests a role for dopamine in early visual development.

The word amblyopia is derived from the Greek word "amblys" for dull and "ops" for eye; hence meaning a dullness of vision. Clinically, it is defined as a best corrected visual acuity worse than 20/40. It is estimated to affect up to 5% of the population(1). Functional amblyopia, is the most studied type of amblyopia and is defined by von Noorden (2) as a reduced visual acuity without ophthalmoscopically detectable anomalies of the fundus. The reduced visual acuity is attributed to a functional cause, rather than to an organic one. Functional amblyopia develops as a result of unequal and/or confusing visual input from the two eyes to the striate cortex. Visual confusion results from unilateral strabismus, where the foveas of the two eyes are aimed at different positions in space resulting in retinal rivalry and an adaptation through suppression and subsequent amblyopia in the strabismic eye. In form vision deprivation, through conditions such as anisometropia (high unequal refractive error) ,cataracts, opaque cornea, vitreous clouding and prolonged uncontrolled patching, the foveas project to a common visual direction but the retinal image from one or both eyes is out of focus producing unequal visual input(1,3). A postnatal critical period of susceptibility to amblyopia is a common factor in all forms of functional amblyopia(1-4). The limits of this critical period in humans, unlike the monkey and the cat, are not known. Many authors approximate this period to occur from birth to about seven years of life(1,4). For monkeys and cats the critical period occurs from one to sixteen weeks and three to four months respectively(5-7). It is during this period when early abnormal visual experience can permanently alter normal visual maturation. This almost "now or never " process of vision in this period is when the proper formation of connections are most reliant on proper and adequate visual stimulation. The earlier the visual deprivation, and the more severe, the

worse the damage to the visual system; and yet the earlier the treatment, the better the prognosis. Conditions that are amblyogenic in children under seven will not cause amblyopia in older children and adults(1,4), and treatment is most effective during this critical period. It seems then that the brain is more "plastic" during this period.

Many clinical and animal studies are aimed at understanding the mechanism involved in the neural plasticity during this critical period, in the hopes of preventing , treating and reversing functional amblyopia. Physiological and anatomical studies of visual deprivation in cats and monkeys have provided models of the mammalian visual system to further understand the nature of normal and abnormal visual development. Visual deprivation in the form of monocular lid suture, binocular lid suture and enucleation made for important discoveries about the development and plasticity of the visual system. Visual deprivation through whatever form has its manifestations in the lateral geniculate nucleus(LGN) and the striate cortex. In normal cats and monkeys, there are ocular dominance columns in the striate cortex consisting of a columnar arrangement of parallel bands of about 400μm in width; formed from the segregation and uniform distribution of geniculocortical afferents from left and right eye input at layer IVc not dependent on visual experience(8-11). The cells in layer IV are monocularly driven; and those outside are binocularly driven(12).

Monocular lid suture, the most studied form of visual deprivation, characterize amblyopia in its severity. Monocular deprivation(MD) in early life of cats and monkeys, produce morphological and physiological changes in the lateral geniculate nucleus and the striate cortex. Changes in the LGN are secondary to cortical changes and are mainly morphological from the cell to the axon terminal(13-17). Cells in deprived geniculate laminae are smaller

than those of the nondeprived eye but have normal physiological responses to stimulation of the deprived eye(7,8,16). The terminals from the deprived pathway afferents are smaller and end on smaller spines which can make synaptic potentials less effective in driving the postsynaptic cell(14). These changes in the LGN can account in part for the inability of the deprived eye to stimulate cortical neurons. In spite of the cell shrinkage in the LGN there is not an associated cell atrophy in layer IVc of the striate cortex (8,10,11) suggesting that monocular deprivation affects the cortex and the LGN differently. The striate cortex is more severely affected by monocular deprivation in that there is a loss of binocular cells; and very few cells can be driven by the deprived eye(7,9-11). There is a shrinkage of the ocular dominance stripe of the deprived eye and an expansion of stripes of the non deprived eye(10,11,18). These changes in the ocular dominance columns are virtually permanent, occur rapidly and at a critical post natal period of susceptibility(10,11). If the deprived eye is unsutured so that both eyes are exposed to light, there is no change in the cortical columns. However, with reverse suturing(the deprived eye is opened and the non-deprived eye is sutured), there is an expansion of the columns of the once deprived eye and a contraction of the nondeprived eye columns(19,20). It seems that it is not enough to just restore activity to the deprived eye but the activity must be greater than that from the nonderived eye. The expansion of the columns of the deprived eye through reverse suture suggests two theories for the development of the ocular dominance shift in monocular deprivation.

The first is that binocular competition in monocular deprivation causes the underactive weak geniculocortical afferents from the deprived eye to become permanently displaced(8,18,21). Reverse suturing results in the active sprouting and regrowth of these cortical afferents from their shrunken

zones into regions of cortex from which they had previously been removed(10,19). Clinically, this theory of binocular competition implies an irreversible loss of visual function. The alternative theory is that binocular inhibition results in the suppression of physiologically active deprived afferents by the nondeprived eye; and in reverse suture there is a release of this suppression(19,20). Since the inputs from the once deprived eye are now more active than the previous nondeprived eye, there could be a strengthening of pre and post synaptic afferents(21). Crawford, et al (22), suggests there is a reorganization of cortical connections rather than a loss of neurons. Perhaps the release of suppression precedes the sprouting and regrowth of axons. The clinical implications for the reversal of amblyopia based on the latter theory are much more favorable. Furthermore, many neurochemical studies seem to support the binocular inhibition theory. Norepinephrine(NE) and Gamma aminobutyric acid(GABA) are the earliest neurochemicals studied with respect to cortical plasticity in the visual system.

Several lines of evidence suggest that GABA is an inhibitory neurotransmitter involved in intracortical inhibition in mammalian visual cortex(23-26). GABAergic inhibition has a fundamental role in determining orientation and direction sensitivity of visual neurons in the striate cortex of cats(23,24,26,27). Following from evidence of GABAergic inhibition, many experiments were carried out to determine the role of this inhibiton in the suppression of afferent inputs from the deprived eye by the non deprived eye and in the development of an ocular dominance shift from monocular deprivation during the critical period. To test the influence of intracortical GABAergic inhibition in cortical plasticity, a GABA antagonist, bicuculline was used. Disinhibition by bicuculline should in theory reduce the ocular dominance shift by releasing the suppression of afferent inputs from the

deprived eye. All of the studies using intravenous and iontophoretic application of bicuculline in cats reared under abnormal monocular experience showed a reduction in the ocular dominance shift and a restoration of binocularity influenced by blockade of GABAergic inhibitory synapses.(24,25,28-30). Furthermore, Silito et al.,(28,30) found that some of the cells in the dominant eye receive input from the nondominant eye which are suppressed by a selective GABA- mediated process.

Mechanisms have been proposed as to the role of GABAergic inhibition in the formation of ocular dominance shift. First, Duffy et al.,(29) suggest that there is an active GABAergic inhibition of deprived eye afferent inputs and consequently, the associated amblyopia will not result in permanent irreversible loss of visual function. However, Silito et al.,(28)suggest that GABAergic inhibition has a passive role in formation of ocular dominance columns. They believe that the "redistribution" of excitatory inputs at the cortex is more significant in the development of the ocular dominance shift in monocular deprivation. Further support from Mower, et al.,(25) showed that GABA inhibition in visual cortical ocular dominance columns is enhanced in animals reared under abnormal monocular experience and is functionally biased by changes in excitatory connectivity and magnifies these changes to produce the overall pattern of physiologically abnormal ocular dominance columns. Ramoa, et al., (24) have shown that bicuculline infusion reduced the selectivity of cortical cells, which allowed them to respond to a larger range of stimuli. Consequently they propose that reduction of cortical plasticity with bicuculline infusion is due to an increase probability of correlated activity between spontaneous discharge from the closed eye and cortical activity evoked by open eye afferents. This theory follows the Hebbian model of synaptic transmission modulation by temporal

correlation between pre- and post synaptic activity (31). Although all of the above studies show that bicuculline can decrease cortical plasticity and the formation of ocular dominance shift as a result of abnormal monocular experience, they all have indicated that GABAergic inhibition is not the only mechanism at work in the formation of ocular dominance shift.

Kasamatsu and Pettigrew(32-33), and Pettigrew and Kasamatsu(34), showed that intraventricular injection during the critical period in monocularly deprived kittens, of the neurotoxin 6-hydroxydopamine (6-OHDA) specific for catecholaminergic cells (i.e. noradrenergic and dopaminergic) reduced cortical plasticity and prevented the formation of the ocular dominance shift. Subsequent work using intracortical microinfusion of 6-OHDA showed a consistent decrease in cortical plasticity(35-38). Furthermore, Gordon, et al.,(39) showed behavioral evidence for the reduction of cortical plasticity in monocularly deprived kittens where the acuity of the deprived eye was better on the first day after eye opening in those kittens treated with intraventricular 6-OHDA.

Strong evidence suggesting a role of NE in cortical plasticity came from the NE intracortical infusion studies which increased plasticity in a dose dependent manner in monocularly deprived kittens previously treated with either intraventricular or intracortical infusion of 6-OHDA; and decreased binocularity in monocularly deprived adult cats outside the critical period (33,40,41). Furthermore, Kasamatsu et al.,(42) found that increasing endogenous norepinephrine levels through electrical stimulation of the locus coereleus could produce an ocular dominance shift in monocularly deprived adult cats, with no prior treatment of 6-OHDA.

To further investigate the mechanism of NE in cortical plasticity. Kasamatsu and Pettigrew(43-45) studied the effect of ß-adrenergic receptors

using an antagonist, D,L,propranolol. Perfusion of this antagonist into kitten visual cortex prevented the formation of an ocular dominance shift in monocularly deprived cats(45). They found that there was a concentration dependent effect on suppressing cortical plasticity(46). Ontogenic studies of ßadrenoreceptor binding by Shaw, et al.,(47,48) and Jonsson and Kasamatsu (49) showed that the maturation of ß-adrenergic receptor binding follow the time course of the critical period in cats. They found that receptor binding peaked at about 7-9 weeks reaching a value 150% of adult, and from 11 weeks on the binding maintained a constant adult value. In comparison with the catecholamine levels which increased 12-13 times in concentration from infancy to adult and continued to increase in adult. These results gave good evidence of the possible role of ß-adrenergic receptors in NE mediated cortical plasticity. Evidence of the cellular events initiated by ß-adrenergic activation, came from the findings by Kasamatsu(50) that intracortical infusion of dibutyryl cyclic adenosine monophosphate, a chemical analog of cAMP, increased plasticity in kittens treated with 6-OHDA. From the above studies, Jonsson and Kasamatsu (49) have proposed that the effects of NE on cortical plasticity is mediated by a NA-ß-adrenoreceptor-cAMP system in visual cortex.

Although there is much support for the role of NE in cortical plasticity, there are other studies which seem to question this role. Bear, et al.,(37) showed that neonatal kitten given systemic injections of 6-OHDA had a decrease of NE levels but not of cortical plasticity. Furthermore endogenous reduction of NE either through local injections of 6-OHDA into the locus coeruleus(51) or lesions of the catecholaminergic bundles did not suppress cortical plasticity. According to Kasamatsu(46) there are three main factors to consider that can account for the negative findings in the studies. First,

systemic injections of 6-OHDA do not confine the effects of NE to visual cortex and thus cannot provide a cause and effect relationship. Second, the interval between 6-OHDA infusion and MD can variably affect plasticity: with a shorter interval there is greater decrease in cortical plasticity(52), but if the interval is long enough there may be a regeneration induced plasticity of NE terminals or a supersensitivity of NE related receptors(52). Third, Kasamatsu(46) states that the validity of interpreting ocular dominance shifts is affected by factors such as microelectrodes used, the distance between successively recorded neurons and length of electrode track.

As significant as the experiments are, that the catecholamine NE may have an important role in synaptic plasticity in the visual cortex, it is important to take into consideration that the neurotoxin 6-OHDA used in these studies is not only selective for noradrenergic terminals. 6-OHDA taken up from the cerebral spinal fluid has been implicated in the destruction of both dopaminergic and noradrenergic axon terminals in the brain (53,54) . Thus, one cannot rule out the significance of dopamine in studies of NE mediated cortical plasticity in the visual system.

Dopamine is a modulatory neurotransmitter with two receptor subtypes D_1 and D_2 that are opposite in function and account for its effects (55). The D_1 receptor subtype activation results in the stimulation of adenylate cyclase and formation of cAMP; whereas the stimulation of D_2 inhibits adenylate cyclase activity(55,56).

Norepinephrine and dopamine have also been shown to have a neuromodulatory role in cortical excitability in the rat and cat visual cortex(57,58). Norepinephrine and dopamine both decreased the firing frequency of cortical cells and enhanced the signal to noise ratio(57,58). Other immunohistochemical studies provide evidence of dopaminergic

innervation from the ventromedial mesencephalic tegmentum to the visual cortex of rats(53,59) and cats(59,60) found mainly in laminae VI. Functional significance of this innervation is based on laminae VI intracortical and subcortical connections. Input to laminae VI is from LGN. Output fibers from laminae VI project to layer IV and to the LGN. From this, it is suggested that lamina VI serves in the regulation of geniculate afferent activity through dopamine modulation of laminae VI output to layer IV or to the LGN(59). Furthermore, biochemical and radioautographic studies in adult cats and rats show the presence of dopamine in the primary visual cortex independent of noradrenergic neurons and the existence of dopamine binding sites(57,58,61,62). These studies, suggest a possible regulatory role for dopamine in norepinephrine mediated cortical plasticity in the rat and cat. To date in human visual cortex, unlike the cat and rat, the presence of dopamine as a neurotransmitter has not yet been established nor its role in normal and abnormal visual development. The aim of this project is to assess, through autoradiographic techniques, human fetal and neonatal dopamine receptor distributions in the primary visual cortex and compare them to adult human visual cortex, in area 17 of the brain. This study may provide us with basic information necessary to predict changes in chemical circuitry which result from abnormal visual development prior to and/or during the critical period in humans.

MATERIALS AND METHODS

Human brain tissue was obtained through a collaboration with the Dept. of Pathology , Vancouver General Hospital, Vancouver, B.C. from adult individuals who died accidentally or of sudden illness. The condition of the occipital poles and the primary visual area was evaluated visually and accepted if the tissue was less than 12 hours postmortem. Additionally, a check of individuals' available medical records determined if there was a history of neurological disease or an extended anoxic brain state prior to death. In each autopsy case the occipital poles were detached immediately after the brain was removed from the skull. Guided by description of the human primary visual cortex from Braak(63), 2 to 4 cm of gyri surrounding the calcarine sulcus of both hemispheres were dissected away, cut into 4 cm wide tissues blocks and frozen immediately on dry ice. Prior to freezing surface tissue landmark diagrams of each tissue block were drawn for orientation simplicity during sectioning. Finally the tissue blocks were doubly wrapped in saran wrap and aluminum foil, labeled, dated, frozen on dry ice then stored at -80C until ready for sectioning. Tissue blocks were thawed to -20C, oriented perpendicular to the calcarine sulcus for coronal sectioning and cut to a thickness of 16 microns on a Hacker-bright motorized cryostat. Identical serial sections were mounted two at a time onto subbed glass slides and stored at -20C until ready for use.

Cortical blocks came from a 27wk old fetus, a 21 day old neonate and from three individuals aged 22, 41, and 76---all males. All tissues were obtained at autopsy within 12hrs. postmortem. For D_1 labeling, slides were

preincubated for 10 minutes at room temperature in 50mM Tris HCL, 20mM NaCl, 5mM KCL, 2mM $CaCl_2$, 1mM $MgCl_2$, and 10micro-molar sulpiride. For total binding, slides were incubated with 5nM [^{3}H]SCH-23390 and for non-specific binding adjacent slides were incubated with 5nM [^{3}H]SCH-23390 and 10micro-molar SKF-38393. After 1 hour, slides were rinsed twice 10 minutes each in 50mM Tris HCL with pH 7.4 at 4C and air dried. The specific activity of SCH-23390 is 70.91Ci/mmol.

For D_2 labelling, slides were preincubated with 50mM Tris, 154mM NaCL, 10mg/L Bovine Serum albumen with pH of 7.4 at room temperature for 10 minutes. Slides were incubated with 2.5nM [^{3}H]-spiroperidol(SPD) for specific binding and other slides with 2.5nM [^{3}H]SPD and 100micro-molar of sulpiride for non specific binding at room temperature for 80 minutes.

After film exposure, tissue sections were Nissl stained or developed for cytochrome oxidase activity and laminae appropriately identified architecturally(63). The autoradiograms were quantified using an MCID image analysis system Imaging Research Inc. St. Catherines, Ontario, Canada to determine relative [^{3}H]SCH-23390 binding densities within laminae. Standards used were Amersham [^{3}H] microscales in the range of 3.03 to 109.08nCi/mg. Films were densitized using an MCID Imaging Research Inc.(St. Catherine's Ontario, Canada) image analysis system to determine binding capacities within laminae as described elsewhere(64).

RESULTS

This is an investigation of the relative distributions of D_1 and D_2 receptors in fetal, neonatal and adult visual cortex using the ligand [^{3}H]SCH-23390 to visualize D_1 receptor binding and using the ligand [^{3}H]SPD to visualize D_2 binding. Nonspecific binding was high at 60% of the total[^{3}H]SCH-23390 and [^{3}H]SPD.

Figure1(a-e) shows D_1 [^{3}H]SCH-23390 binding on coronal sections of primary human visual cortex from the 5 different ages. At the fetal age of 27 weeks laminae patterns are not observed. Homogenous D_1 binding exists at this age throughout the occipital pole. High but diffuse binding on the upper cortical layers is observed. In the D_1 21 day old neonate a high density of cortical binding can be seen surrounding the calcarine sulcus with moderate binding in noncortical white matter areas. In the adult (Fig. 1 cde) heavy homogeneous D_1 [^{3}H]SCH-23390 binding occurs in all cortical laminae. Within area17 a dense band is visible. This layer, laminae IVcß is the primary input layer for thalamocortical afferents from the geniculate nucleus.

Figure2(a-e) shows D_2 [^{3}H]SPD binding on coronal sections from the same 5 subjects. At the fetal age of 27 weeks(fig.2a) moderate binding occurs in the superficial layers with low to moderate D_2 binding occurring in the deeper layers. Overall less binding exists for D_2 receptors than D_1. In the neonate layer IVcß is distinctly visible unlike that for D_1 while binding in other layers remains the same. There is moderate binding in some portions of layer II and III but not in others, a possible section thickness variation. Again high density of D_2 receptors are definitely found in the supragranular region of cortex surrounding the calcarine sulcus. In the adult(Fig. 2c-e), D_2 binding is similar to D_1, with homogenous binding in all cortical laminae and lamina IVcß distinctly visible.

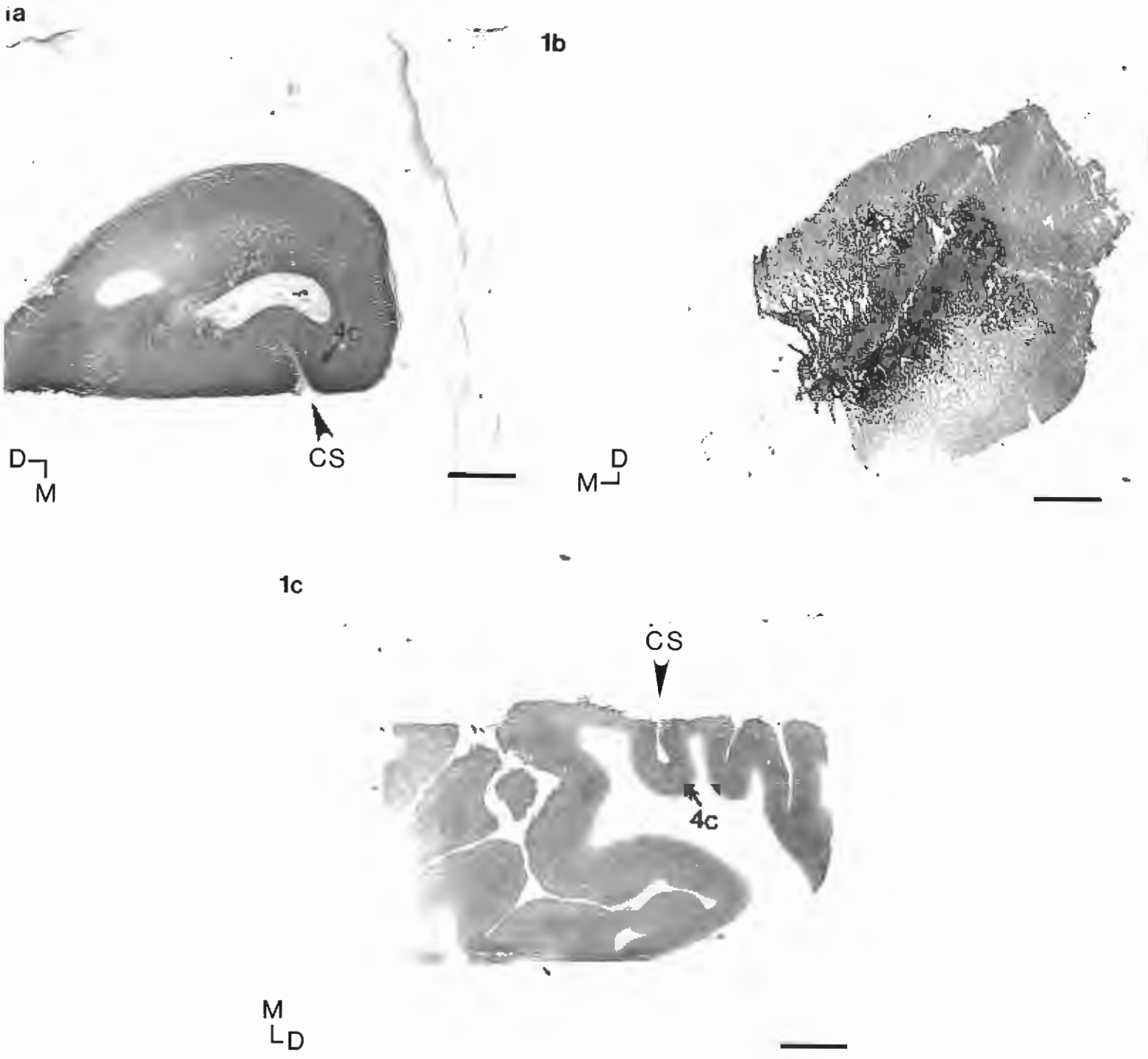

FIGURE 1

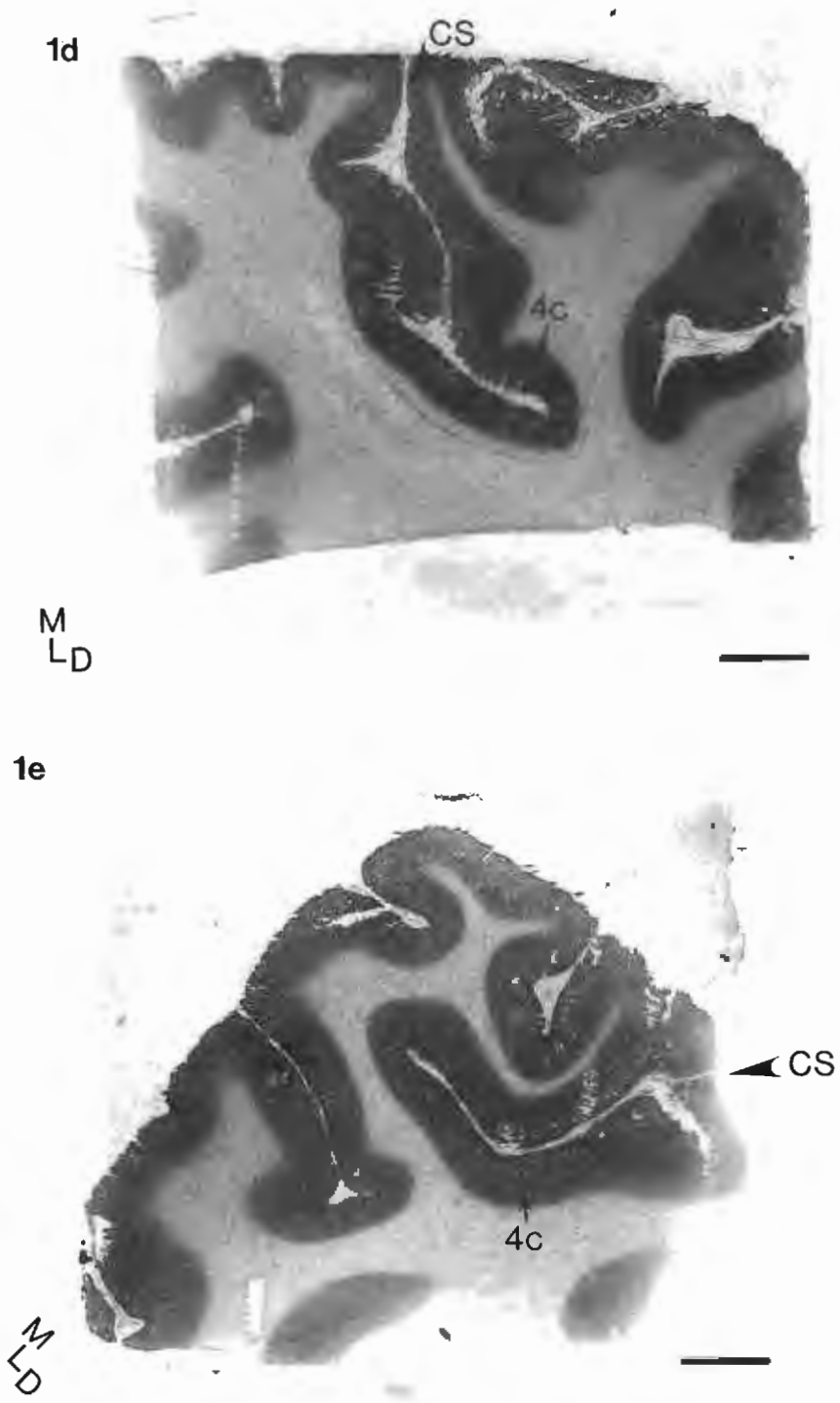

Figure 1: Distribution of D_1 receptors in human visual cortex. a-27 week old fetus. b-21 day old neonate. c-e: adults ages 41, 76, 22 respectively. D is dorsal, M is medial, CS is calcarine sulcus. Bar is 5mm.

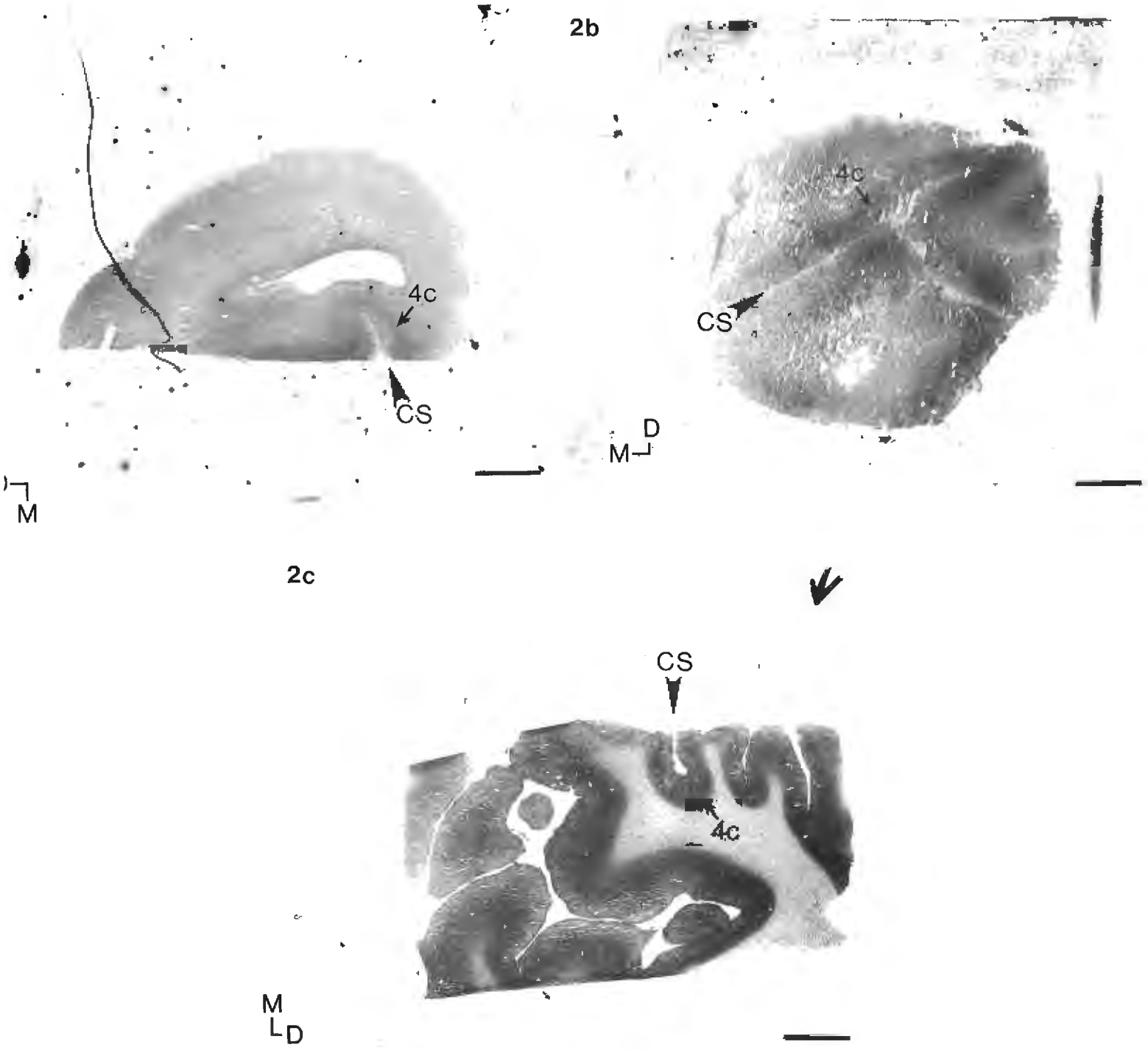

FIGURE 2

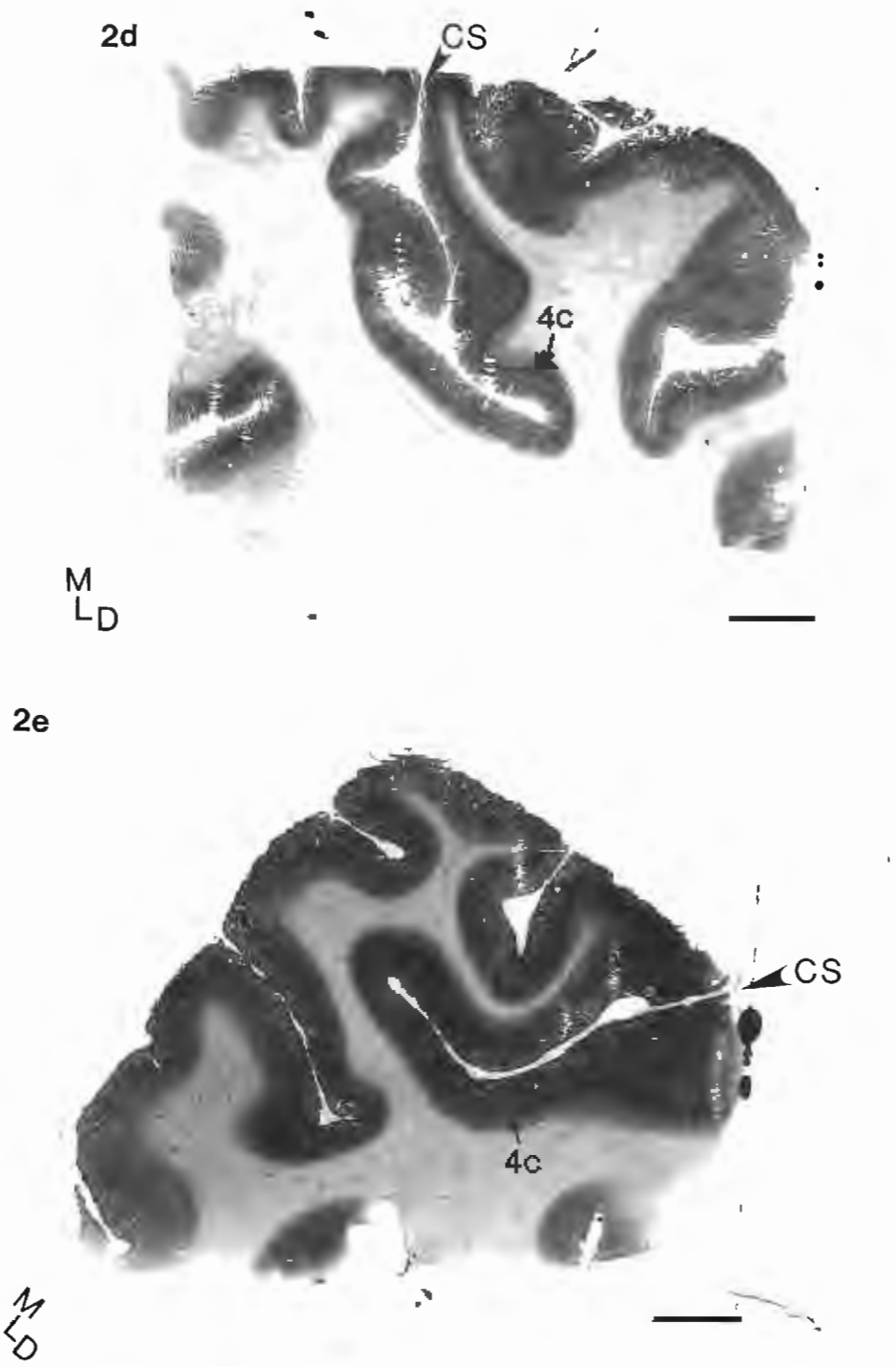

Figure 2: Distribution of D_2 receptors in human visual cortex. a-27 week old fetus. b-21 day old neonate. c-e: adults ages 41, 76, 22 respectively. D is dorsal, M is medial, CS is calcarine sulcus. Bar is 5mm.

DISCUSSION:

This preliminary study shows a laminar and ontogenic distribution of both D_1 and D_2 receptors in human visual cortex. Unlike that found in cat and rat where no binding is observed in the geniculate input layer(59,61), the most significant result of this study is IVcß binding of both D_1 and D_2 in adult visual cortex. Binding is more distinct in layer IVc, than in all other layers for all ages .

One might conclude from these experiments that D_1 receptors are found in the superficial layers early in gestation and move in to the deeper layers in the period prior to 21 weeks of life. At 21 weeks postpartum, more homogenous moderate binding is observed. Later, laminar changes occur, possibly during the critical period, whereby higher binding is seen in laminae IVc. This new D_1 distribution is maintained throughout adult life. D_2 binding is similar to D_1 at 27 weeks gestation. D_2 has significant binding in the superficial layers and lower to moderate binding on the deeper infragranular layers III-VI. In the 21 day old neonate D_2 binding is significantly different than D_1; there is a distinct IVc band of D_2 receptors. This implies a different, possibly more significant, role for D_2 receptors in early visual development than D_1 receptors. This pattern of D_2 receptors continues through until adulthood.

Similar autoradiographic studies have also shown the presence of D_1(65) and D_2(66) receptor binding sites in adult and child human visual cortex. Unlike this present study, Cortes et al.(65) and Camps et al.(66) have found higher relative dopamine binding in the deeper layers for both age groups and no significant binding occurring in the geniculate input layer IVc for both D_1 and D_2 receptors. The reasons for this discrepancy are not clear and thus indicates the need for further investigation.

The presence of dopamine receptors in fetal visual cortex may suggest a role for dopamine in early visual development. Elaboration of this study with emphasis on ages within the critical period and in comparison with amblyopic human visual cortex matched age to age would provide a better opportunity to understand the receptor changes which occur in association with abnormal visual experience and the effects of dopamine in the chemical circuitry involved with neural plasticity. Until it is established that dopamine is a neurotransmitter in the human visual cortex and post mortem amblyopic human tissue pre and post critical period is available to study, we must depend on information derived from rat and cat visual cortex on which to suggest a modulatory role for dopamine in NE mediated cortical plasticity and abnormal visual development in humans.

In conclusion, although at present there is no pharmacological treatment for amblyopia, the current treatment is early diagnoses and early intervention. Through vision training and lenses, we as primary care practitioners can improve, in some cases significantly, the quality of vision and visual perception in amblyopic patients.

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AUTOBIOGRAPHY

Marina Roma received her Bachelors degree in biology from the University of British Columbia in Vancouver in May 1988. She will receive her Doctor of Optometry degree from Pacific University in 1994. She plans to practice in Vancouver Canada. Her future plans include returning to the Philippines and providing voluntary eye care.