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THE NEUROPHYSIOLOGICAL EFFECTS OF AGING ON TEMPORAL PROCESSING IN THE VISUAL CORTEX

by

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A thesis submitted in conformity with the requirements for the degree of M.Sc.

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ABSTRACT

Aging can produce a decline in the ability to process visual motion. This decline is due in part to a slowing in temporal processing, the locus of which may reside in the central visual system. This study used critical flicker fusion (CFF), or the frequency of flickering light required to produce an appearance of steady light, to compare temporal processing in visual cortical neurons in young (2 – 4 months) and old (24 – 28 months) Long Evans Hooded rats. It was hypothesized that a slowing in cortical temporal processing would result in decreased physiological CFF thresholds in old subjects. CFF thresholds were significantly reduced in old animals in both primary and secondary visual cortex and in simple, complex, and hypercomplex cells. This study provides the first indication of a neurophysiological difference in temporal processing speed in the aging visual cortex that may underlie behavioural observations of reduced CFF in elderly observers.

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ABBREVIATIONS

AL	Anterolateral
AM	Anteromedial
ANOVA	Analysis of variance
C	Celcius
CFF	Critical flicker frequency
cm	Centimeter
CNS	Central nervous system
dLGN	Dorsal lateral geniculate nucleus
FFT	Fast Fourier Transform
ft-L	Footlambert
g	Gram
hr	Hour
Hz	Hertz
i.p.	Intraperitoneal
kg	Kilograms
kHz	Kilohertz
LI	Laterointermediate
LL	Laterolateral
LM	Lateromedial
M	Mole
MRI	Magnetic resonance imaging

ABBREVIATIONS CONTINUED

mg	Milligram
ml	Milliliter
msec	Millisecond
Oc1M	Primary occipital cortex, monocular
Oc1B	Primary occipital cortex, binocular
Oc2L	Secondary occipital cortex, lateral
Oc2ML	Secondary occipital cortex, medial lateral
Oc2MM	Secondary occipital cortex, medial medial
PM	Posteromedial
PSTH	Peri-stimulus time histogram
sec	Second
χ^2	Chi-square
µm	Micrometer
µsec	Microsecond

1.0 INTRODUCTION

1.1 Age-related visual deficits

As we age, our visual functioning usually deteriorates. This deterioration is commonly associated with diseases of the visual system such as cataract, glaucoma and macular degeneration, or with an increase in lenticular density or yellowing of the lens. These age-related visual deficits are highly variable, progress at different rates, and result from a variety of genetic and/or environmental influences (Sekuler, 1991). Optical changes however, can not account for all age-related visual deficits and some deficits may be a result of changes within central visual pathways (Spear, 1993). That central structures also contribute to age-related visual deficits is exemplified by elderly individuals who demonstrate no signs of ocular pathology, and who perform well on clinical tests of visual acuity, yet still complain of poor vision. These visual "underachievers" indicate the necessity of studying both the behavioural and neurophysiological effects of age on visual processing within the entire visual system.

1.2 Visual temporal processing and aging

1.2.1 Human studies: One aspect of vision that appears to decline with age is the ability to detect temporal change, or dynamic visual acuity (Sekuler & Sekuler, 1992). For instance, temporally contiguous visual stimuli that young subjects see as separate and distinct entities, may appear smeared or blurred to elderly subjects (Kline, 1987). Kline and Schieber (1982) suggested that age differences in temporal resolution are a consequence of an older nervous system that is slower to recover from the effects of short-term stimulation. A decline in temporal resolution produces age-related deficits on most visual tasks designed to measure the perception of moving stimuli (Kline, 1987), however, it can also account for the superior visual performance of elderly observers in at least one task of temporal processing. Kline and

Orme-Rogers (1978) constructed common three letter words that could be presented in their entirety, or sequentially as two corresponding word-halves that were unrecognizable when viewed separately. Young (18 - 21 years) and old (59 - 78 years) observers were able to correctly identify all of the words at 0 msec interval, and the performance of both groups declined as the interstimulus interval between presentation of the temporally contiguous word halves was increased. However, the elderly observers outperformed the young subjects as the interstimulus interval was increased. The superior performance of the older subjects was attributed to a lack of temporal resolution in the senescent visual system and subsequent persistence of stimuli within the central visual system (Kline & Orme-Rogers, 1978).

The ability to process temporally contiguous visual stimuli is important in everyday vision for the perception of moving targets (Kline, Babbitt, Fozard, Kosnik, Schieber & Sekuler, 1992). A deficit in this process can manifest itself as an increase in vehicle accidents involving elderly drivers who are unable to either accurately judge their own speed, or the speed of surrounding vehicles (Kline et al., 1992). Unfortunately, studies examining such age-related deficits in visual temporal processing lag behind those on spatial acuity. The tremendous social impact and psychological effect on the self-esteem of elderly individuals who must surrender their driver's license and cope with other lifestyle changes related to an inability to perform temporal processing (Salvage, 1995), indicates the critical need for study regarding these deficits.

There is currently little information as to how changes in neuronal information processing and integration could contribute to this apparent age-associated decrease in the rate of temporal processing. Kline, Scialfa, Lyman and Schieber (1990) suggested that the temporal sluggishness of the senescent visual system may be due to a transient/sustained shift.

or a greater decline with age in the effectiveness of "transient", as opposed to "sustained" channels. Sustained channels are sensitive to high spatial frequencies, respond in a slow and persistent manner, are characterized by an extended temporal integration period and are consequently suited to the perception of form. Conversely, transient channels are sensitive to low spatial frequency stimuli, respond quickly and briefly to stimulus change, and appear to inhibit persisting activity in sustained channels (Kline & Schieber, 1982).

Kline et al. (1990) tested the hypothesis of a transient/sustained shift by presenting vertical sinusoidal gratings of six spatial frequencies to young (18 - 24 years) and old (56 - 72 years) observers. Grating-pairs of the same spatial frequency were presented with decreasing interstimulus intervals until the gratings were reported as continuous. Grating continuity increased with increasing spatial frequency for both age groups, and no age difference in perceived continuity was observed with high spatial frequencies. However, older adults required significantly greater interstimulus intervals than young subjects to discriminate lower spatial frequencies. The authors suggested that the age difference in detecting the offset of low spatial frequency gratings isolated a decline in the temporal effectiveness of transient channels. The results could not be attributed to age differences in the ocular media as acuity actually favoured the older participants, and any optical blur would have affected high and not low spatial frequencies. A transient/sustained shift in visual processing could account for the slowed visual processing speed and poor detection of stimulus change observed in the elderly (Kline, 1987). This work indicates the involvement of central systems in producing age-related behavioural changes in visual functioning, however it cannot specify the exact neural location of the observed changes.

1.2.2 Animal studies: Animal studies are critical for examining the neurological effects of aging in the visual system. In non-human primates, the transient and sustained channels correspond to the magnocellular (motion sensitive) and parvocellular (form) pathways respectively. Spear (1993) suggested that a greater age-associated decline in magnocellular functioning would have two effects on temporal processing: a decrease in sensitivity to a wide range of temporal frequencies, and a reduction in temporal response dynamics to high temporal frequencies. In an attempt to localize age-related neuronal changes in these two systems, Spear, Moore, Kim, Xue, and Tumosa (1994) studied spatial and temporal processing in the dorsal lateral geniculate nucleus (dLGN): the main relay station between the retina and visual cortex, in rhesus monkeys. No significant differences were observed between the neural responses of young (5 - 16 years) and old (25 – 28 years) animals in latency, amplitude, spatial-frequency resolution, optimal spatial frequency, high temporal frequency cut-off, temporal frequency bandwidth or contrast. The only significant difference was an increase in mean spontaneous discharge rate, and a decrease in optimal temporal frequency in the parvocellular neurons of old animals. However, even these differences were small and thought to reflect random variation rather than reliable changes in dLGN functioning due to aging.

Further support that the retino-geniculate pathway is relatively unaffected by aging comes from anatomical studies. Kim, Tom and Spear (1996) reported no significant age-related decrease in retinal ganglion cells in the rhesus monkey, nor has a significant loss of neurons been reported with age in the dLGN of monkeys (Ahmad & Spear, 1993) or rats (Satorre, Cano & Reinoso-Suarez, 1985). Due to the inability of these initial studies to isolate age-associated changes in the early stages of visual processing, this study examined age-

related changes in temporal processing further up the visual pathway in primary and association visual cortex.

1.3 Comparisons with auditory temporal processing

Age-related deficits in temporal processing have also been observed in the auditory system. for instance. the ability to discriminate temporally modulated pairs of clicks declines in old age (Weis. 1963). The cortex has also been implicated in the deficits in auditory temporal processing. Robin and Royer (1989) reported that the elderly can experience deficits in speech perception independent of the changes in the peripheral structures that produce high frequency hearing loss. To determine the involvement of the auditory cortex in age-related changes. Ricketts and Mendelson (1997) used extracellular single cell recordings to compare temporal processing of dynamic stimuli in young (3 – 4 months) and old (22 – 24 months) Long Evans Hooded rats. They reported that the majority of cells recorded from young rats responded best to fast frequency modulated sweeps whereas those from old rats preferred slow speeds. suggesting a deficit in temporal processing speed in the aged auditory cortex.

1.4 Age-associated cortical slowing

Erikson. Hamlin. and Breitmeyer (1970) suggested that the inability of the senescent cortex to resolve temporal changes in stimuli may reflect a concomitant slowing of information processing that occurs as an organism ages. Slowing within the central nervous system is believed to be one of the ubiquitous and significant changes associated with old age (Birren. Woods & Williams. 1979; Salthouse. 1990). The development of modern stereological techniques and counting methodology has revealed that. contrary to previous reports (Devaney & Johnson. 1980). the slowing of information and temporal processing cannot be attributed to a loss of neurons in the aged cortex. Pakkenberg and Gundersen (1997) reported a non-

significant (10 %) reduction in neuron number in the aged human brain. Similarly, a study on the striate cortex of the rhesus monkey by Peters, Nigro and McNally (1997) found no indication that thickness, volume or number of neurons is altered by age. Any deficits in visual functioning due to cortical processing cannot therefore be accounted for by a decrease in neuron number and instead, may be attributed to changes in dendritic tree structure and/or spine density (Spear, 1993). Unfortunately, there is little information as to how changes in neuronal structure exert specific effects on the information processing capabilities of aged neurons.

1.5 Critical flicker frequency

The apparent slowing in information processing may reflect a general cortical aging mechanism that could produce the deterioration in temporal processing in the aging visual system. A commonly used analytical tool for studying temporal processing is critical flicker. Repeated stimulation of the retina by flashes of light at a certain rate is called "flicker" and critical flicker frequency (CFF) is the frequency of flickering light (measured in cycles/sec or Hz) required to produce an appearance of steady light to an observer (Misiak, 1947). At a slow rate of flicker, each flash can be perceived separately; however as the rate is increased, it becomes increasingly difficult to dissociate one flash from the next. When the intermittent light is presented at a rate at which the flashes appear superimposed, the stimulus is perceived as steady illumination and referred to as the point of fusion. The ability to perceive a certain number of flashes per unit time provides an index of the efficacy of the visual system's temporal processing capabilities (Brozek & Keys, 1945). Because critical flicker is not highly correlated with visual functions such as acuity, critical flicker can be regarded as a sensitive measure of temporal processing within the visual system (Brozek & Keys, 1945; Kline 1990).

1.5.1 Behavioral measures of CFF: Critical flicker has been utilized frequently in behavioural studies to assess and compare temporal resolution and processing across species. There has, however, been variation in the values of CFF reported in separate laboratories. Schwartz and Cheney (1966) reported cat CFF to range from 45 to 70 Hz. Loop and Berkley (1975) found the range to be 40 to 55 Hz and Taravella and Clark (1963) found the highest frequency that could be discriminated by cats was 65 Hz. These slight discrepancies can be accounted for by the use of different intensities of the stimulating light because the ability to distinguish between flicker and fusion has consistently been shown to increase with increases in luminance (Loop, Petuchowski & Smith, 1980). Changes in luminance produce similar changes in behavioural CFF thresholds in cats, dogs, monkeys and rats (Williams, Pollitz, Smith & Williams, 1985; Coile, Pollitz & Smith, 1989).

1.5.2 Scotopic and photopic CFF: It is possible to isolate the influence of scotopic and photopic processing by altering the level of luminance and determining the corresponding CFF thresholds. A break in the CFF/luminance function is apparent with decreasing luminance that has been attributed to a shift from cone to rod vision (Loop et al., 1980). Williams et al. (1985) reported the presence of a rod/cone break in the CFF/luminance curve of the albino rat. Rods supported the perception of flicker up to 21 Hz at scotopic intensities ranging to -1.3 log (ft-L) and cones supported a maximum flicker perception of 39 Hz with increased luminance to 2.7 log (ft-L). In comparison, the rods of cats support the discrimination of flicker at frequencies as high as 35 Hz (Loop et al., 1980) and in dogs, scotopic CFF reaches 40 Hz (Coile et al., 1989). In humans scotopic CFF ranges from 18 to 28 Hz (Coile et al., 1989). With increases in luminance, photopic CFF is around 70 Hz in humans, 85 Hz in dogs (Coile et al., 1989) and 65 Hz in cats (Loop et al., 1980).

1.5.3 CFF and aging: One method by which critical flicker can be used to study the effects of aging is to compare the differences in CFF threshold between young and old subjects. CFF threshold corresponds to the fastest rate of flicker apparent to the observer preceding the appearance of steady light or fusion. Psychophysical studies with humans have found a negative correlation between age and the number of flashes/sec at which fusion occurs (Brozek & Keys, 1945; Misiak, 1947; McFarland, Warren & Karis, 1958; Lachenmayer, Kojetinsky, Ostermaier, Angstwurm, Vivell & Schaumberger, 1994). Brozek and Keys (1945) found little change in the point of fusion up to the age of 40, after which a constant decrease in CFF with age was observed. In comparison, Misiak (1947) found a regular decline in CFF threshold from young subjects (mean age 23) who perceived steady illumination at 47.1 flashes/sec to older subjects (mean age 74) who perceived fusion at 38.3 flashes/sec, though individual variation was great. More recently, Lachenmayer et al. (1994) described a linear decline in CFF thresholds over the entire age range from 9 to 86 years of age, even after correction for pupil size. Differences in the recruitment of subjects, exclusion criteria and testing procedure may account for some of the observed differences between studies.

1.5.4 CFF and the CNS: Although these studies revealed a consistent difference between young and old subjects with respect to temporal processing, and particularly to CFF thresholds, due to their behavioural design, information regarding the locus of CFF processing is limited. Although CFF was previously thought to rely solely on retinal functioning, it is apparent that central visual systems, in particular the cortex, constrain the perception of flicker and fusion (Simonsen & Brozek, 1952; Spear, 1993). Evidence that barbituates and alcohol depressed CFF values provided early evidence that CFF was related to the excitability of the CNS (Simonson & Brozek, 1952). Naturally occurring damage to the occipital lobes in

humans (Battersby, 1951) and experimentally induced lesions in cat (Taravella & Clark, 1963; Schwartz & Cheney, 1966) and monkey (Mishkin & Weisenkrantz, 1959) visual cortex have produced reduced values of CFF, indicating the involvement of the cortex in processing CFF. Walker, Woolf, Halstead, and Case (1943) conducted electroencephalogram recordings in response to flickering light in anaesthetized monkeys. They found that the visual cortex could only be driven at a maximum rate of 34 Hz, compared to 62 Hz in the optic nerve and 59 Hz in the lateral geniculate which were above the reported maximum values for fusion. The authors suggested that temporal processing in the cortex, as opposed to the retina, lateral geniculate body, or optic nerve limited the temporal resolving power of the primate visual system. The neural changes affecting CFF may originate in the apparent age-related "transient-sustained shift" in visual processing mentioned earlier. A deficit in transient channels, which are maximally responsive to rapid stimulus change such as flicker, could produce the age-associated decline in cortical CFF (Kline, 1987).

1.6 Applicability of the aging rat and CFF

A decline in the ability to perceive high frequency flicker with age is well documented and therefore CFF provides an appropriate tool to begin an examination of the neural mechanisms underlying changes in temporal processing in the aged visual system. This study examined the response of neurons in the aging rat visual cortex to CFF. The rat was selected as an appropriate experimental animal as it has a relatively short life span and the normal functioning and anatomy of the young rat visual system has been extensively studied, making a direct comparison to the aging system possible. It is also possible to control confounding variables inherent in human studies of aging where young and old subjects may differ not only in visual ability but also in health status, education and medication intake. Flickering stimuli

can be considered to have real world meaning for the rat because processing flickering stimuli is critical for the detection of prey such as fluttering insects, and for the avoidance of quickly looming predators (Dean, 1990).

1.7 Anatomy of rat visual cortex

On the basis of myelo- and cytoarchitectonic studies, Zilles (1985) divided the rat visual cortex into primary (Oc1) and secondary (Oc2) regions. Oc1 corresponds to area 17 delineated electrophysiologically in the gray rat by Espinoza and Thomas (1983). Zilles (1985) divided Oc1 into monocular (Oc1M) and binocular (Oc1B) regions that receive contralateral and binocular input respectively. These subareas can be recognized in Nissl and myelin stained sections by a higher cell density in combination with a lower myelin density in Oc1M compared to Oc1B (Zilles, 1990). Oc1 represents about 50 % of visually responsive cortex and about 10% of total neocortical surface area (Espinoza & Thomas, 1983). A major source of input to Oc1 is from the dLGN, with the majority of afferents terminating in layer 4 and lower layer 3, with some reaching layers 1 and 6 (Sefton & Dreher, 1985). Lesions of Oc1 produce a loss in the ability to perform pattern discriminations in behavioural tests, indicating the involvement of Oc1 in the analysis of stationary spatial contrast of stimuli in the central visual field (Dean, 1990).

Zilles (1985) divided Oc2 into lateral (Oc2L), medial lateral (Oc2ML) and medial medial (Oc2MM) areas. Oc2L corresponds approximately to area 18a that was delineated by electrophysiological mapping studies and contains at least four visuotopically organized maps of the visual field, namely lateromedial (LM), anterolateral (AL), laterointermediate (LI) and laterolateral (LL) (Espinoza & Thomas, 1983). Electrophysiological studies have recorded overlapping auditory and visual responses in Oc2L (McDonald & Mascagni, 1996) and a

multimodal function for Oc2L is also indicated by connections from both the somatosensory and secondary auditory area (Kolb, 1990). Behavioural tests of pattern discrimination indicate that Oc2L is also involved in the analysis of stationary spatial contrast in central vision (Dean, 1990). Zilles (1990) reported that Oc2M is contrasted with the other occipital areas due to a reduction in myelination. Oc2M corresponds to area 18 or 18b and contains two electrophysiologically defined visuotopic maps, namely anteromedial (AM) and posteromedial (PM) (Espinoza & Thomas, 1983). Dean (1990) reported that lesions to Oc2M interfere with the detection of transient stimuli throughout the visual field and the analysis of peripheral cues for navigation.

There are extensive cortico-cortical connections in the rat with reciprocal projections between Oc1 and Oc2L and Oc2M (Thomas & Espinoza, 1987; Coogan & Burkhalter, 1993; Shao & Burkhalter, 1996). Forward projections from Oc1 terminate in layers I through VI in Oc2, while feedback projections from Oc2 to Oc1 lack strong input to layer IV and instead terminate in layers I, II, III, V, and VI (Coogan & Burkhalter, 1993). In the rat, as found in the cat, a large variety of pyramidal and nonpyramidal cells project to the contralateral visual cortex where they may contribute to the receptive features of contralateral cells (Martinez-Garcia, Gonzalez-Hernandez & Martinez-Millan, 1994). There are distinct lamina-dependent projections (Bourassa & Deschenes, 1995) between the visual cortical areas and the visual dorsal thalamic nuclei through distinct visual thalamic reticular nuclei regions (Lozxadi, Gonzalez-Soriano & Guillery, 1996; Coleman & Mitrofanis, 1996). Although the visual cortex of the rat is far from homogenous, there is little consistent evidence that the existence of distinct anatomical areas provides an anatomical substrate for the segregation of various visual tasks. As well, there have been no aging studies conducted to determine whether age affects

the hierarchical organization of the visual system. The current study therefore includes the separate analysis of single neurons in both primary and secondary visual cortical areas in order to contribute to our understanding of aging within the cortex.

1.8 Receptive fields of visual cortical neurons in the rat

The receptive fields of cells in rat visual cortex show strong functional resemblance to those found in the cat (Hubel & Wiesel, 1962) and monkey (Hubel & Wiesel, 1968). Simple, complex and hypercomplex cells have been identified in the rat, although unlike in the cat and monkey, each type of receptive field receives direct input from the dLGN (Zilles, 1990). In the rat, there is no evidence for distinct laminar distribution, except for simple cells, which are found predominantly in layer IV (Parnavelas, Burne & Lin, 1983). Although this organization argues against the hierarchical model of visual processing proposed for non-human primates, it does indicate that neurons in the rat are capable of processing basic visual stimuli in a similar manner to other species.

Parnavelas et al. (1983) examined the functional properties of morphological types of neurons in the primary visual cortex (area 17) of the Long Evans rat. They reported that complex cells (44%) were pyramidal and located in layers II through VI. Simple cells (27%) were both pyramidal and non-pyramidal and located in layers II, III, and IV and hypercomplex cells (13%) were pyramidal and situated in layers II, III, and V. Sixteen percent of the visual cortical cells were classified as non-orientated which have not been reported to concentrate in any particular cortical layer (Sefton & Dreher, 1985). While the functional properties of visual cortical neurons are well established in the rat and other species, there is no evidence as to how aging may effect the classification and/or response of specific neurons. This study is therefore the first to examine how aging may alter the functional properties of single cells by comparing

the temporal processing capabilities of simple, complex and hypercomplex cells in the rat visual cortex.

1.9 Purpose and hypothesis

The purpose of this thesis was to provide the first evidence of any neural mechanisms underlying age-related temporal processing deficits in the visual system by comparing the response of neurons in the visual cortex of young and old rats to CFF. No studies have compared the response of individual neurons in the visual cortex to CFF, or have compared how aging affects the functional properties of visual cortical neurons. By examining the response of neurons to CFF in both primary and secondary visual cortex, this study is therefore the first to consider whether anatomy and temporal processing are related in a systematic way in both the young and aged rat. The hypothesis was that an age-related slowing in temporal processing at the neuronal level would result in decreased threshold values for CFF in old as compared to young animals. The similarities between laminar organization, receptive field types, distinct visual areas and cortico-cortical connections in the rat and other species, suggest that findings regarding basic visual temporal processing may indicate similar processing in higher species.

2.0 METHODS

2.1 Subjects

Subjects were thirty-six male Long Evans hooded rats obtained from Charles River Laboratories, Canada. Young subjects (n = 28, 180 – 450 g) ranged between two and four months of age (average 3.2 months). Old subjects (n = 8, 475 – 700 g) were retired breeders who arrived at the lab at six months and ranged from 24 to 28 months (average 25.9 months). Due to variable housing conditions across laboratories, including diet and exercise, it is

difficult to determine the life expectancy of the Long Evans rat. In our laboratory, young subjects reach their adult weight by six months though they are able to reproduce at a much earlier age. An increase in death rate is observed from 22 months.

Subjects were housed individually in standard laboratory cages in a colony room on a 12 hour light/dark cycle with access to food and water *ad libitum*. Experiments were run during the light cycle. The optics of the eyes was checked regularly with an opthalmoscope to exclude any subjects with signs of optical pathology such as cataracts.

2.2 Apparatus

***2.2.1 Flicker*:** Whole field stimulation was provided by light pulses delivered by a Grass PS33 PLUS stimulator lamp that was enclosed in foam rubber to muffle the click that accompanied each light flash. The lamp was positioned 40 cm from the animal's eye and located outside a window that was part of an electrically shielded, sound-attenuating chamber. Flicker frequency could be varied between 1 and 60 Hz in increments of 1 Hz by a Macintosh Quadra 950 computer. The duration of each light pulse was 10 μsec and the response of the cell to individual presentations was recorded for 1 sec. Between pulses, no visual stimulation was presented. The intensity of the flash illuminator was set to step 8 on the Grass photic stimulator's scale of 1-16, which corresponds to a luminance value of 17 cd/m^2 as measured by a Hagner Universal S2 Photometer.

***2.2.2 Receptive Fields*:** Classification of a neuron's receptive field properties were determined by presenting bars of light by an Electrohome EDL 58XL projector onto a dark screen placed at a distance of 30 cm from the animal's contralateral eye. This distance was chosen to correspond to that used in other experiments which have examined the visual system of the rat (Wiesenfeld & Kornel, 1975; Parnavelas, Burne & Lin, 1981). A Macintosh Quadra

950 computer manipulated stimulus size, direction, orientation and speed to determine the parameters that evoked the best response in each cell. Data were collected and stored using the A/Dvance software package.

2.3 Procedure

***2.3.1 Surgical Procedure*:** The surgical procedures employed in this study have been approved by the Canadian Council for Animal Care (CCAC) and comply with the stipulations regarding the care and use of experimental animals set out by the American Physiological Association. Subjects were weighed and anaesthetized with Equithesan (3 mg/kg, i.p.) and administered 0.2 cc atropine sulfate subcutaneously to prevent respiratory distress. Body temperature was maintained at 37°C by a heating blanket and monitored by a rectal probe. Glycerine-based eyedrops (Isoptotears) were administered periodically to prevent the corneas from drying out. Subjects were placed in a modified head holder to allow unobstructed visual stimulation and the right eye was kept open with sutures (one to the upper and one to the lower eyelid). No corrective lenses were used and the eye was left undilated to record the natural response of the visual system. A constant infusion of Equithesian (1 mg/kg/hr) in lactated ringer's solution was administered throughout the course of the experiment to ensure a proper level of anesthesia and hydration.

Following a midline incision and removal of the fascia overlying the occipital cortex, all wound margins and pressure points were generously infiltrated with the long-lived local anesthetic bupivicanine hydrochloride (2.5 %). A craniotomy was performed over the left occipital cortex using the stereotaxic coordinates of Paxinos and Watson (1986). Dura matter was left intact and bathed with silicone oil (Dow Corning C.) to prevent it from drying out and to reduce any pulsations. Because the rat has laterally positioned eyes, at the completion of

surgery the animal was placed so that the long axis of the body formed a 110° angle with the stimulus to facilitate whole field stimulation.

2.3.2 Electrical recording: All recordings were made in a totally darkened room where the only source of light was from the stimulus display. Extracellular single-unit responses were recorded by randomly sampling the entire visual cortex (defined cyto-architectonically as primary area 17 and secondary areas 18a and 18) with glass-coated, platinum-iridium microelectrodes (impedance 0.7 - 2.1 M at 1.0 kHz) that were advanced orthogonally through the cortex by a hydraulic microdrive (Kopf). Neuronal activity was amplified, band-passed filtered (BAK A-1B Electronics amplifier), and monitored on an oscilloscope (Tektronix) and audiomonitor (Grass). Spike activity was separated from background noise with a level discriminator (BAK DS1 window discriminator). Stimulus and spike event time were collected, displayed as peri-stimulus time (PSTH) histograms, and stored by a Macintosh Quadra 950 computer.

To ensure a random sampling of the entire visual cortex, individual penetrations were separable by a distance visible to the naked human eye. As well, to reduce bias imposed by possible columnar organization, no more than three cells, separated by a minimum of 100 μm, were recorded from each penetration.

2.3.3 Critical flicker frequency threshold: Once a visually responsive cell was isolated, the critical flicker frequency threshold was assessed by pseudo-random presentation of the flickering stimulus at frequencies varying between 1 and 60 Hz. PSTH histograms displayed the neural response as spikes/sec in 5 msec bin widths, allowing analysis of the temporal relationship between the stimulus and neural response. Data were collected across 20 successive presentations of each frequency with an interstimulus interval of two to four

seconds depending on the response of the cell. An intertrial interval of one minute was imposed before presentation of the next frequency. The cell was said to entrain to the stimulus when it was able to respond separately to each flash of light and the frequency was increased until the cell could no longer entrain to each flash of light. It was evident that the cell could no longer entrain when it responded randomly throughout the presentation of the stimulus, or responded to the train of flashes as a single pulse of light by displaying a discrete response corresponding to the onset and/or offset of the stimulus.

2.3.4 Receptive field types: Wherever possible, a qualitative analysis of the receptive field properties of each cell was undertaken. To capture a visually responsive cell, a bar of light was presented monocularly to the contralateral eye and moved across the entire visual hemifield at various speeds, directions, and orientations. Once the location and boundaries of the receptive field was delimited, the cell was identified as either simple, complex, or hypercomplex based on criteria previously established by Hubel and Wiesel (1962, 1968) and adapted for the rat by Parnavelas et al. (1983). Simple cells were characterized by their low background discharge rate and relatively small receptive fields compared to complex cells. When a bar of light was increased in length within the receptive field, simple cells displayed response summation or an increase in firing response. Antagonism between excitatory "ON" and inhibitory "OFF" regions within the receptive field was also characteristic of simple cells. In comparison, complex cells were distinguished by their active background discharge rate, the absence of response summation, and the ability to record "ON" and "OFF" responses to a bar of light situated anywhere within the receptive field. Hypercomplex cells were classified according to the characteristic property of end-stopping, that is, they displayed a reduction in

response frequency when an optimally oriented bar of light was elongated beyond the excitatory region of the receptive field.

2.3.5 Analysis of CFF threshold: The CFF threshold for the cell, or the frequency at which the cell could no longer entrain to each flash of light, was determined qualitatively by a modified staircase procedure. This involved randomly increasing or decreasing the frequency of the stimulus in variable increments. For example, if a cell could entrain at 5 Hz, 10 Hz and 15 Hz but not at 20 Hz, the intervening frequencies were presented in random order, for example, 18 Hz, 16 Hz, 19 Hz and then 17 Hz. Once the CFF threshold was determined, the frequency values surrounding threshold were run again to reduce any time of presentation effects and to obtain an average threshold response. The spontaneous discharge rate of the cell was determined by a 0 Hz condition that was recorded by turning the stimulator lamp off.

After all the data were collected, to quantify response magnitude at each frequency, MATLAB 5.1 performed Fast Fourier Transforms (FFT) of each histogram. The power at the fundamental frequency was computed for each stimulus. For comparative purposes, and to account for any changes in CFF threshold with the increase in luminance associated with higher flicker rates, the normalized power (power at fundamental frequency divided by the average response rate) was computed. Two curve fitting procedures were applied to each transform: a linear regression and an exponential fit. In the linear regression, CFF threshold was defined as the frequency at which the regression line crossed the frequency axis. For the exponential curve, CFF was defined as the frequency yielding a response that was 20 % of the peak response. While the various procedures resulted in small differences in absolute CFF, there was no effect on the pattern of results, thus CFF is reported as the linear regression of the power at the stimulus fundamental frequency.

The mean CFF threshold values for young and old subjects were compared for statistical significance using the two-tailed Student's t-test for independent samples and significant relationships were analyzed using chi-square and analysis of variance (ANOVA).

2.3.6 Histology: After the CFF threshold was determined, selected cells were lesioned (6 μA for 6 sec) for histological verification. After completion of the recording session, the subjects were deeply anaesthetized with an intraperitoneal injection of somnitol and perfused transcardially with 0.1 M phosphate buffered 0.9 % saline (200 ml) followed by 3.9 % paraformaldehyde in 0.1 M phosphate buffer (500 ml). The brain was immediately removed from the skull and stored in paraformaldehyde. Before freezing, the brains were left overnight and shaken in 25 % sucrose for cryoprotection. Coronal sections of the visual cortex were cut in 40 μm sections by a freezing microtome and mounted on gelatin-coated slides. The slides were left to dry overnight before being stained with cresyl violet and coverslipped with Permount. The sections were viewed under a light microscope and the site of electrode tracts and the location of lesioned cells identified with reference to the atlas of Paxinos and Watson (1986) and Zilles (1985).

3.0 RESULTS

Extracellular recordings were made from 113 neurons in rat visual cortex: 68 of which were from the 28 young animals (average 2.4 per animal) and 45 from the 8 old animals (average 5.6 per animal). The results revealed a significant difference in the way cells recorded from the visual cortex of young and old rats responded to critical flicker.

3.1 Critical flicker frequency threshold

3.1.1 Young: Figure 1a illustrates an example of one type of flicker response recorded from a complex cell in a young animal. At frequencies below 15 Hz the cell was entrained to

the flickering stimulus and discrete bursts of spike activity corresponding to every flash are apparent on the histograms. At 15 Hz the cell was entrained to the first 13 of 15 flashes but did not respond in a similar manner to the fourteenth and fifteenth flash. At 16 Hz it was only able to follow the first 10 flashes. The response of the cell was dramatically different above 16 Hz. At 17 Hz no entrainment was evident and instead, the cell responded vigorously after the last flash in the trial in a characteristic "OFF" manner to a fused light stimulus. The CFF threshold of this cell was therefore determined as 16 Hz. The FFT corresponding to this cell is displayed in Figure 1b.

Figure 2a illustrates a different kind of response recorded in a young animal. This cell was classified as complex with a biphasic response because it responded more than once in rapid succession to a single light flash. Visual inspection of the histogram determined that at frequencies above 30 Hz, the cell could no longer respond synchronously to the flicker stimulus and instead responded primarily to the onset of the stimulus and randomly throughout the rest of the stimulus presentation. Quantitative analysis by the linear regression of the power at the stimulus fundamental frequency in the FFT (Figure 2b) confirmed the CFF threshold as 31 Hz.

Figure 3a illustrates a complex cell recorded in secondary visual cortex. This cell was able to entrain to frequencies up to 20 Hz but responded primarily to the onset of the stimulus at frequencies of 22 Hz and above. The CFF threshold of this cell was thus 21 Hz and confirmed by FFT (Figure 3b). A CFF threshold of 21 Hz was representative of the average CFF threshold recorded in young animals.

3.1.2 Old: Figure 4a illustrates an example of a cell recorded from an old animal. In both the qualitative and quantitative analysis, this cell exhibited a CFF threshold of 8 Hz. The

cell was able to entrain to each flash of light up to, and including, 7 Hz (although as flicker frequency was increased the response of the cell diminished). At 8 Hz it was only able to respond to the first few flashes of the trial and at 9 Hz and above, it displayed a characteristic "ON" response to a fused light stimulus and responded randomly throughout the rest of the stimulus presentation. Figure 4b illustrates the FFT for this cell.

Figure 5a illustrates another example of a cell recorded from primary visual cortex of an old animal. This cell was classified as hypercomplex with a CFF threshold of 14 Hz. The cell was able to entrain to each flash of light up to 12 Hz and while at 13 Hz it appeared unable to follow the flashes of light, at 14 Hz it was at least able to follow the first 9 flashes. At frequencies above 14 Hz the cell primarily responded to the onset of stimulation and randomly throughout the rest of the presentation. The FFT of the response confirmed the CFF threshold of 14 Hz (Figure 5b).

3.1.3 Comparison of Young and Old CFF: The range of CFF thresholds obtained from neurons recorded across all young subjects was between 10 and 35 Hz, whereas the range recorded across all old subjects was 6 to 15 Hz. The mean CFF threshold for young animals (21.54 ± 6.0 Hz) was significantly higher that the mean CFF threshold for old animals (11.89 ± 2.7 Hz), $t(111) = 10.103$, $p < .001$ (Figure 6).

Due to the unequal number of cells recorded in individual subjects, the raw data was examined for any general trends and to ensure that the response of any individual animal did not bias the average score. In general, the CFF thresholds of individual neurons recorded within a single subject were fairly highly correlated with each other. For example, in young subject number 7 in Appendix A, individual CFF thresholds ranged between 15 and 17 Hz. This trend is striking in the old subjects where, for instance, the range of individual CFF

thresholds in animal number P1 in Appendix B was between 7 and 9 Hz. However, in some animals the range of CFF thresholds was more varied. For instance in young animal number 9 in Appendix A, CFF thresholds ranged between 16 and 33 Hz and in old animal number 2, the range was between 6 and 15 Hz. When each animal was given an individual score for CFF threshold, in young animals the range was between 14 and 31.5 Hz, and in old animals the range was between 8.2 and 13.5 Hz. When the averages of the individual CFF threshold scores were compared, the mean CFF threshold for young animals (22.27 ± 5.66 Hz) was still significantly higher than the mean CFF threshold for old animals (11.54 ± 2.39 Hz), $t(34) = 7.878$, $p < .001$.

3.2 Response Properties

After threshold was reached, three kinds of neuronal responses were recorded in the visual cortex of both young and old animals: 1) "ON", 2) "ON" and "OFF" and, 3) a random response with no peak in spike activity throughout the presentation of the stimulus. A fourth "OFF" response was only observed in 3 neurons recorded in young animals, one of which is displayed in Figure 1a. The type of response was not equally distributed in young, χ^2 (3, $N = 68$) = 74.235, $p < .001$ or old, χ^2 (2, $N = 45$) = 40.533, $p < .001$ visual cortex. The majority of cells in young (46/68) and old (35/45) animals responded in a characteristic "ON" manner to frequencies above CFF threshold similar to that shown in Figures 2a, 3a, 4a and 5a; that is, they responded only to the first flash in the trial. Random responding above CFF threshold was observed in 17 of 68 young neurons and 7 of 45 old neurons. The remaining young (2/68) and old (3/45) neurons responded to both the first flash and the last flash in the stimulus, but not the intervening flashes, above CFF threshold. There was no difference in the distribution of response properties between young and old animals, ($p > .05$).

3.3 Receptive Field Properties

3.3.1 Young: The receptive field properties were determined for 26 of the 68 neurons recorded from young animals. There was an unequal classification of simple, complex, and hypercomplex cells, χ^2 (2, N = 26) = 22.462, p < .001. Fifteen percent (4/26) of the cells were classified as simple, 77 % (20/26) as complex and 8 % (2/26) as hypercomplex. The range of CFF thresholds across all simple cells was 14 to 16 Hz, for complex cells it was 18 to 32 Hz, and for hypercomplex cells it was 26 to 32 Hz. ANOVA indicated a significant difference in mean CFF threshold values recorded between simple (15 ± 1.2 Hz), complex (24.5 ± 4.5 Hz), and hypercomplex (29 ± 4.2 Hz) cells, F (2, 26) = 10.444, p = .001 (Figure 7 - light bars). CFF thresholds for simple cells were significantly lower than in complex, t (22) = 8.214, p < .001 and hypercomplex cells, t (4) = 4.583, p < .05. The difference in CFF thresholds between complex and hypercomplex cells was not significant, p > .05.

***3.3.2 Old*:** Receptive field properties for 20 of the 45 neurons recorded in old subjects were determined. As in young animals, the classification of simple, complex, and hypercomplex cells was significantly different, χ^2 (2, N = 20) = 9.100, p < .05. Twenty percent (4/20) of the cells were classified as simple, 65 % (13/20) as complex and 15 % (3/20) as hypercomplex. The range of CFF thresholds recorded across all simple cells was 7 to 15 Hz, for complex cells it was 6 to 15 Hz, and for hypercomplex cells it was 11 to 15 Hz. In contrast to cells recorded from young animals, ANOVA indicated no significant difference in mean CFF threshold between cells classified as simple (11.0 ± 4.08 Hz), complex (12.69 ± 2.43 Hz) and hypercomplex (12.67 ± 2.08 Hz) in old animals, (p > .05) (Figure 7 - dark bars).

3.3.3 Comparison of Young and Old Receptive Fields and CFF: There were no significant differences between the classification of simple, complex and hypercomplex cells

in young and old animals ($p > .05$). Figure 7 illustrates that mean CFF thresholds recorded in simple, complex and hypercomplex cells in old subjects were all lower than those obtained in young subjects, with simple cells displaying the lowest mean CFF threshold values in both young and old subjects. Analysis of variance indicated that age had a significant effect on receptive field CFF threshold values, $F(1, 46) = 52.724$, $p < .001$, as did the type of receptive field, $F(2, 46) = 9.274$, $p < .001$. A significant interaction was found between age and receptive field classification for CFF threshold values, $F(2, 92) = 5.121$, $p < .05$.

3.4 Cortical Location

3.4.1 Young: It was possible to verify the recording site of 53 of the 68 neurons recorded from young animals: 45% (24/53) were located in primary visual cortex (Oc1M and Oc1B) and 55% (29/53) were in secondary visual cortex (Oc2L, Oc2ML, and Oc2MM). A wider range of CFF thresholds was recorded in secondary visual cortex (14 – 35 Hz) compared to in primary visual cortex (15 - 31 Hz). The mean CFF threshold for neurons in secondary visual cortex (21.33 ± 6.32 Hz) was not significantly higher than that obtained in primary visual cortex (20.42 ± 4.84 Hz) ($p > .05$) (Figure 8 – light bars).

3.4.2: Old: For the old animals, the location of 32 of the 45 neurons was determined. Fifty three percent (17/32) of cells were recorded from primary visual cortex whereas 47% (15/32) of cells were recorded in secondary visual cortex. The range of CFF thresholds recorded in primary (6 – 15 Hz) and secondary (8 – 15 Hz) visual cortex was highly similar. Similar to young animals, in old animals the mean CFF threshold for neurons recorded in secondary visual cortex (12.8 ± 2.11) was slightly higher than in primary visual cortex (11.88 ± 2.87), and this difference was also not significant ($p > .05$) (Figure 8 – dark bars).

3.4.3: Comparison of Young and Old Cortical Location and CFF: Analysis of variance indicted age had a significant effect on cortical CFF values. $F(1, 85) = 60.771$, $p < .001$, whereas location did not ($p > .05$). There was no significant interaction between age and location on CFF values ($p > .05$) (Figure 8).

Figure 1a

A series of PSTHs indicating the response to different rates of flicker (expressed in Hz) by a complex neuron recorded in the visual cortex of a young subject. Time of stimulus presentation (1000 msec), divided into 200 bins of 5 msec, is displayed on the x-axis. Squares below the histograms indicate the timing of flashes. The cell was able to entrain to each flash of light from 1 Hz through 15 Hz and at 16 Hz it was able to entrain to the first 10 flashes. At 17 Hz the cell responded as if the stimulus was a single fused light, displaying a response to the last flash only. The CFF for this cell was 16 Hz and was characterized by an "OFF" response above threshold.

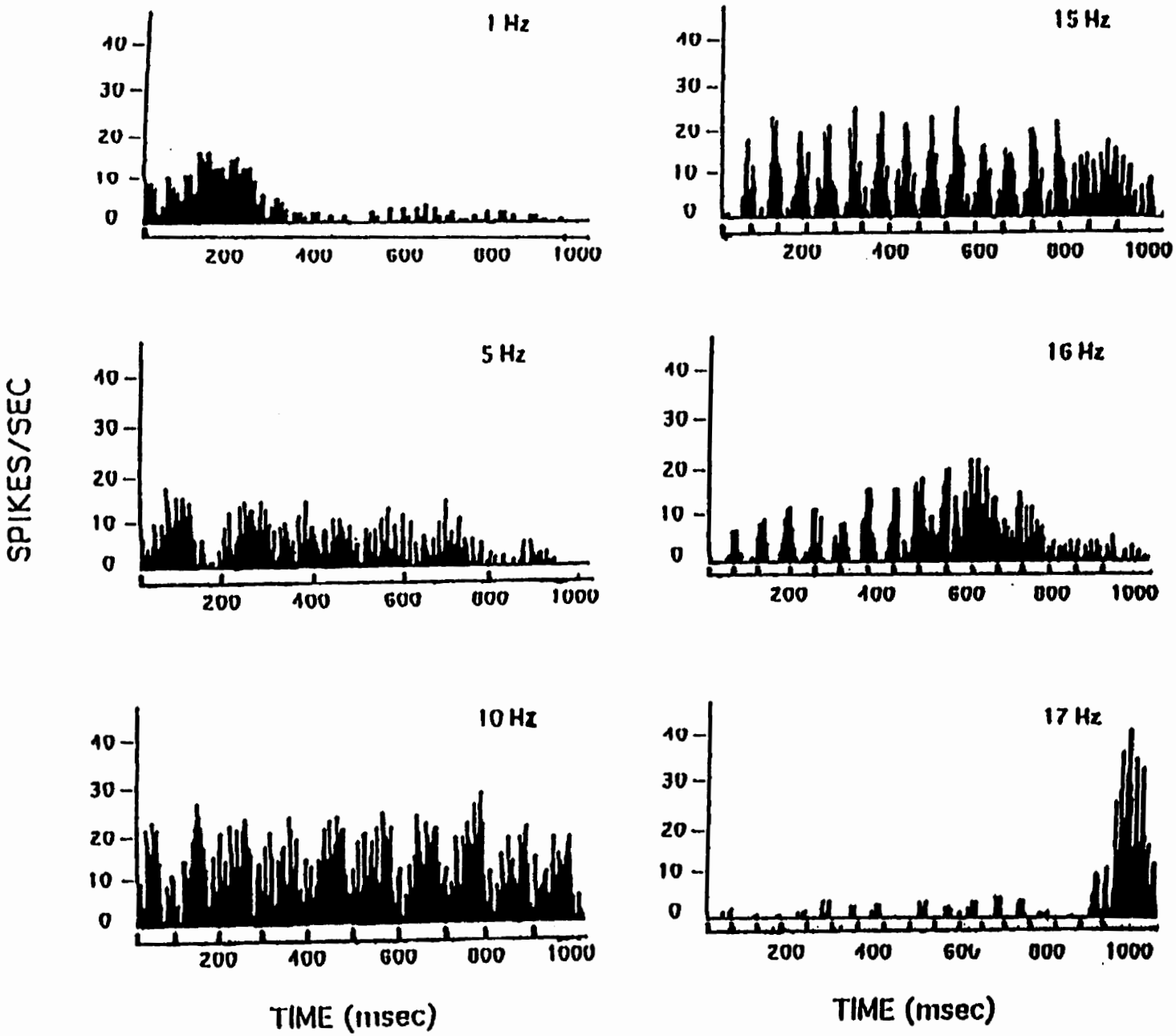

1 Hz
15 Hz
5 Hz
16 Hz
10 Hz
17 Hz
SPIKES/SEC
40
30
20
10
0
200
400
600
800
1000
TIME (msec)
TIME (msec)

Figure 1b

The FFT of the response magnitude of the cell in part a. The linear regression (solid line) and exponential fit (dashed line) are included.

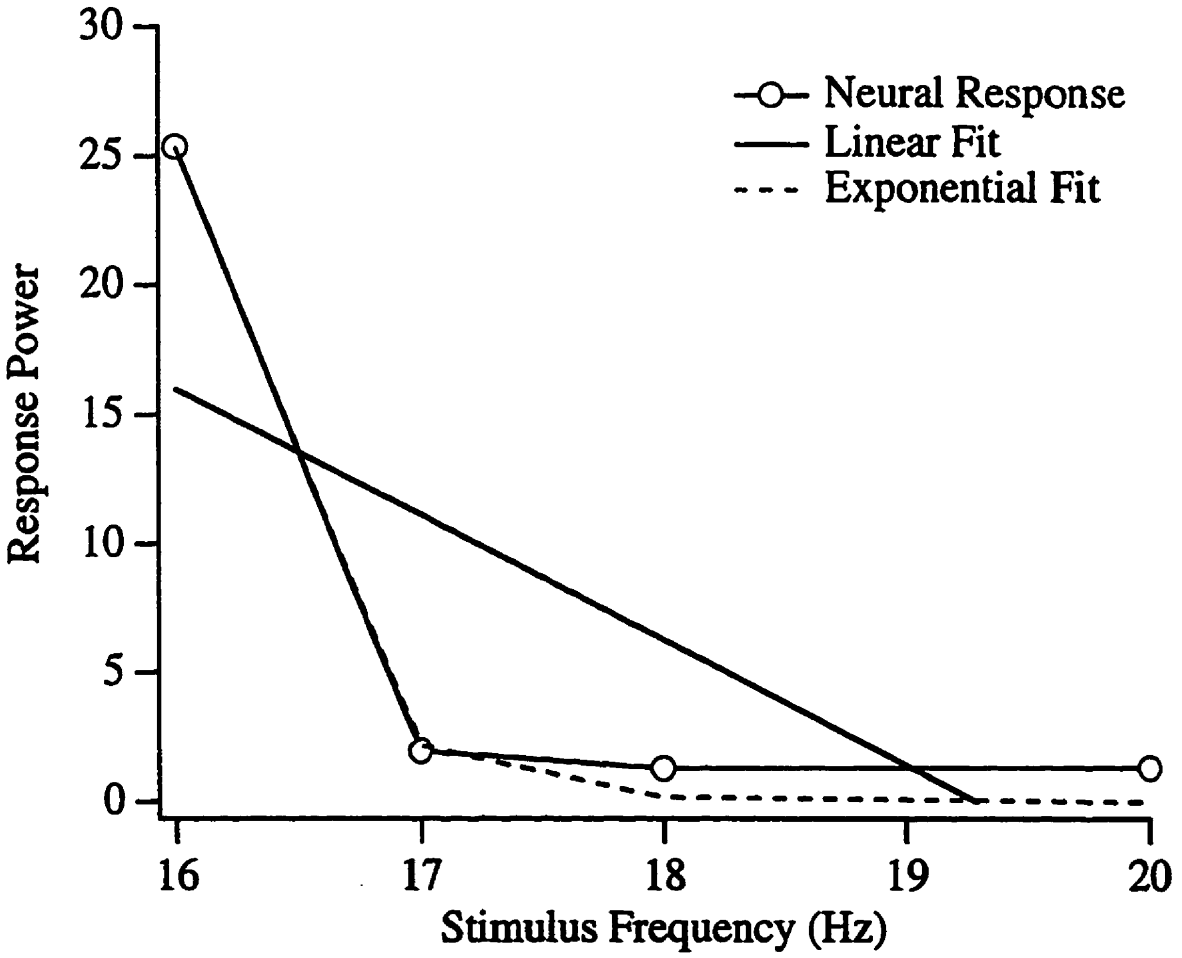

30
25
20
15
10
5
0
Response Power
16
17
18
19
20
Stimulus Frequency (Hz)
Neural Response
Linear Fit
Exponential Fit

Figure 2a

A series of PSTHs indicating the response of a complex cell recorded in the visual cortex of a young subject to increasing rates of flicker. Time of stimulus presentation (1000 msec), divided into 200 bins of 5 msec, is displayed on the x-axis. Squares below the histograms indicate the timing of the flashes. This cell displayed a biphasic response, responding more than once to each flash of light and was able to entrain to frequencies up to 30 Hz. At higher frequencies it displayed an increase in responding to the first flash only. This cell therefore had a CFF threshold of 31 Hz and was characterized by its' "ON" response to frequencies above threshold.

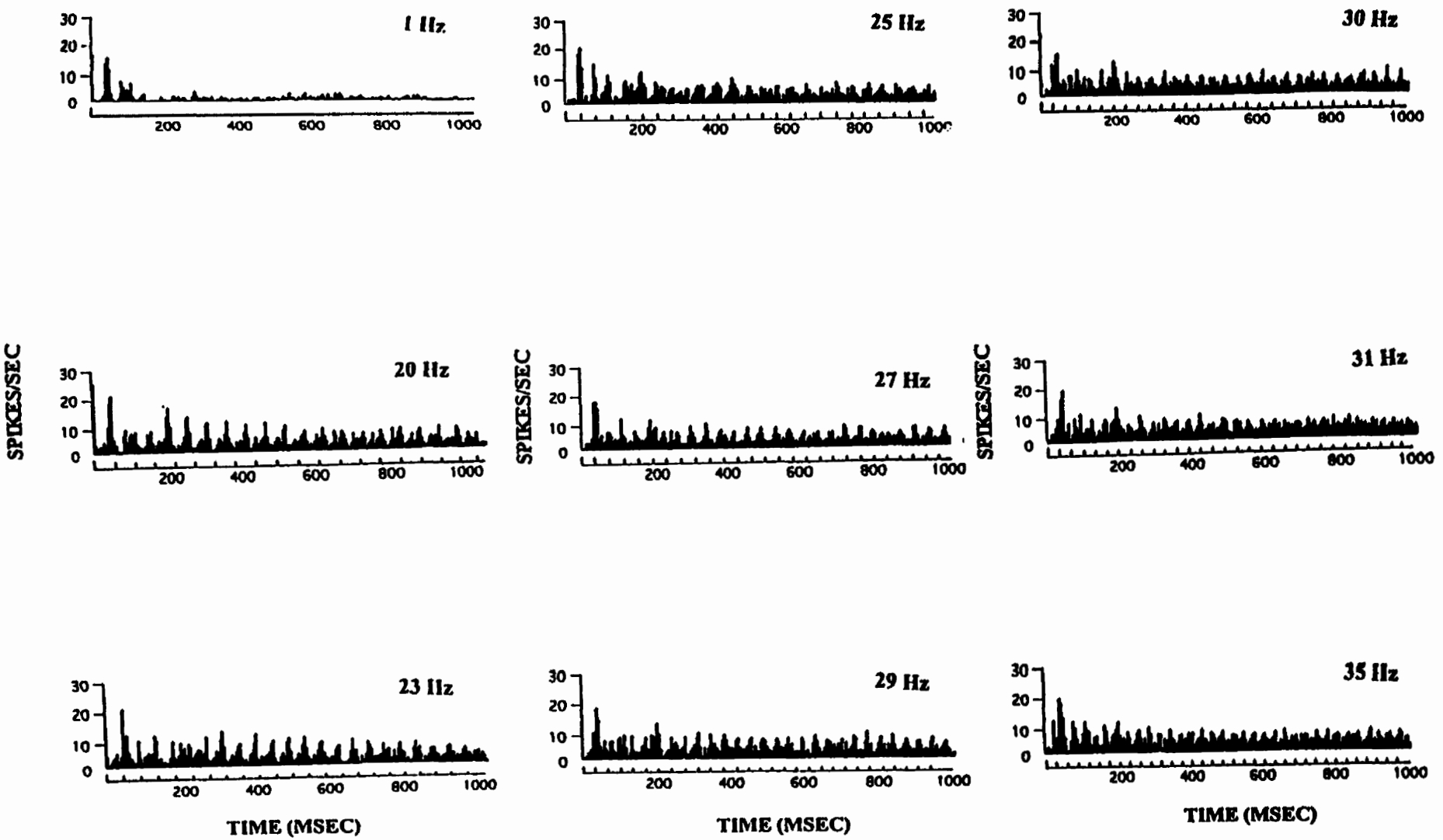

1 Hz
25 Hz
30 Hz
20 Hz
27 Hz
31 Hz
23 Hz
29 Hz
35 Hz
SPIKES/SEC
SPIKES/SEC
SPIKES/SEC
TIME (MSEC)
TIME (MSEC)
TIME (MSEC)
0
10
20
30
200
400
600
800
1000

Figure 2b

The FFT of the response magnitude of the cell in part a. The linear regression (solid line) and exponential fit (dashed line) are included. The linear regression of the power at the stimulus fundamental frequency determined that the CFF threshold of this cell was 31 Hz.

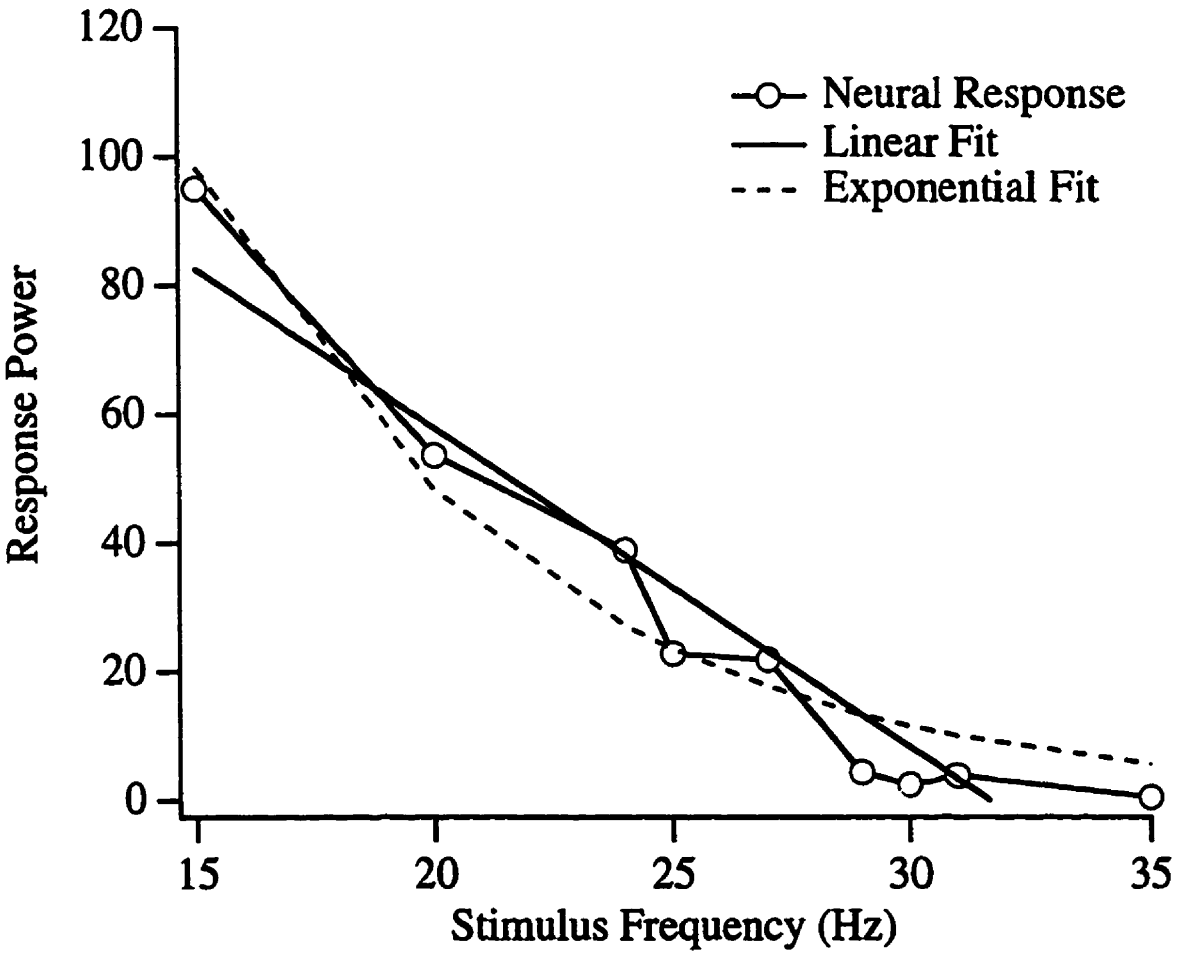

120
100
80
60
40
20
0
Response Power
15
20
25
30
35
Stimulus Frequency (Hz)
Neural Response
Linear Fit
Exponential Fit

Figure 3a

A series of PSTHs illustrating the response of a complex cell recorded in the secondary visual cortex of a young animal. Time of stimulus presentation (1000 msec), divided into 200 bins of 5 msec, is displayed on the x-axis. Squares below the histograms indicate the timing of the flashes. This cell was able to entrain to frequencies up to 20 Hz and at 22 Hz it responded primarily to the onset of stimulation. The CFF threshold of this cell was therefore 21 Hz which was representative of the average CFF threshold recorded in young animals.

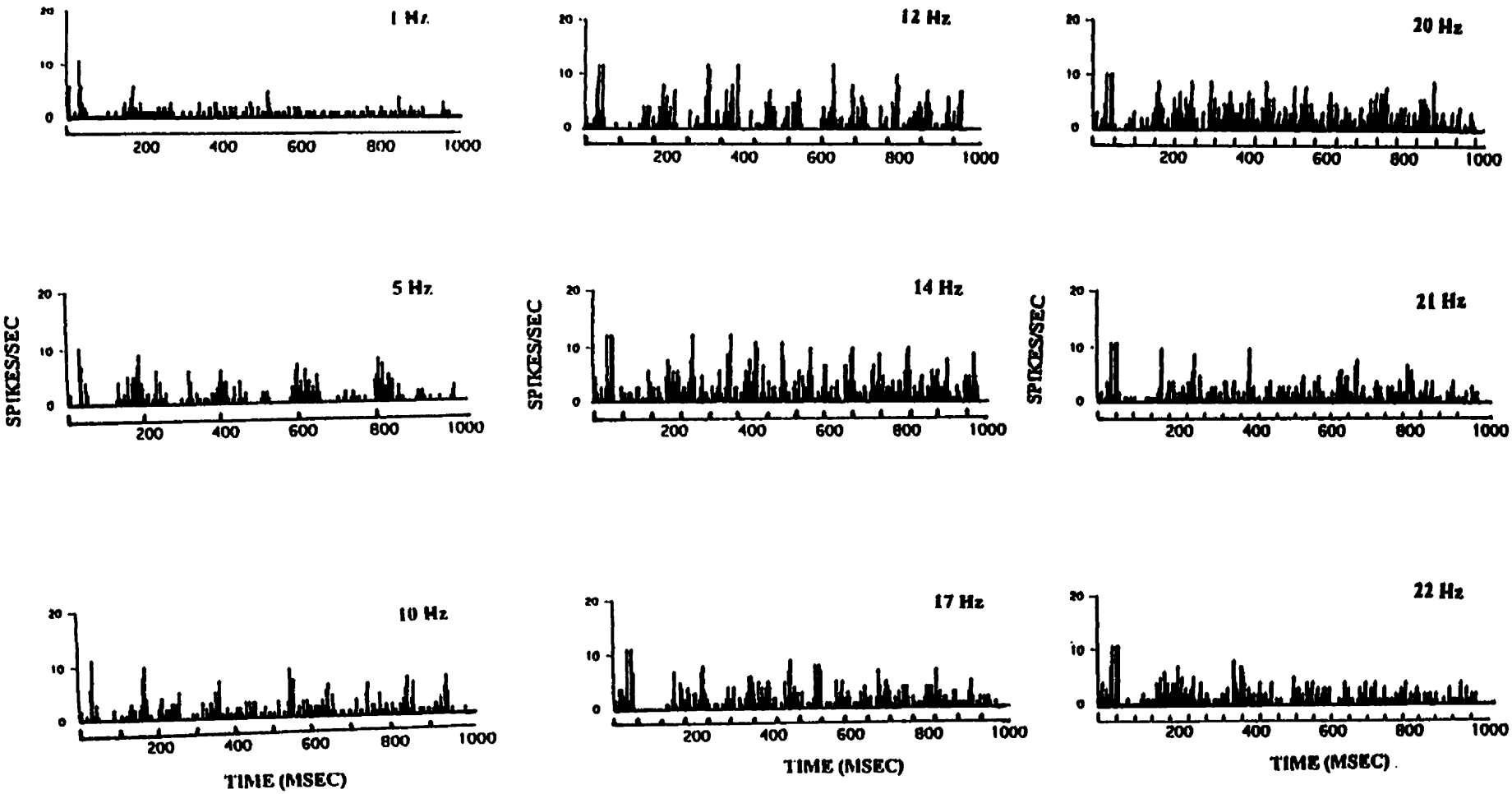

1 Hz
12 Hz
20 Hz
5 Hz
14 Hz
21 Hz
10 Hz
17 Hz
22 Hz
SPIKES/SEC
SPIKES/SEC
SPIKES/SEC
TIME (MSEC)
TIME (MSEC)
TIME (MSEC)
0
10
20
200
400
600
800
1000

Figure 3b

The FFT of the cell in part a. The linear regression of the power at the stimulus fundamental frequency confirmed that the CFF of this cell was 21 Hz.

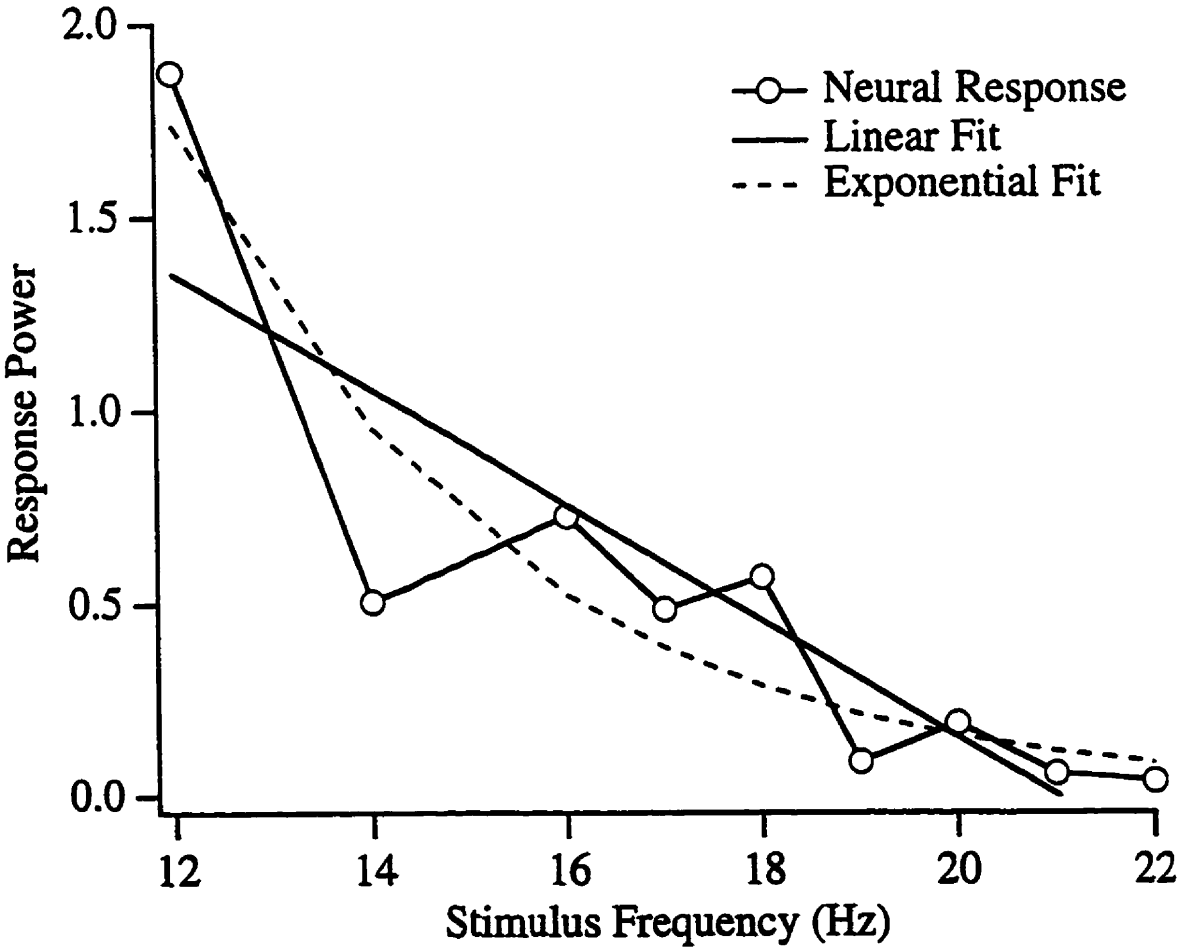

2.0
1.5
1.0
0.5
0.0
Response Power
12
14
16
18
20
22
Stimulus Frequency (Hz)
Neural Response
Linear Fit
Exponential Fit

Figure 4a

A series of PSTHs illustrating the response of a visual cortical neuron recorded from an old subject. Time of stimulus presentation (1000 msec), divided into 200 bins of 5 msec, is displayed on the x-axis. Squares below the histograms indicate the timing of the flashes. At flicker frequencies below 8 Hz the cell was able to entrain to at least the first few flashes, however it was unable to do so above 8 Hz. The CFF threshold for this cell therefore occurred at 8 Hz. Above threshold the neuron was characterized as only responding to the "onset" of the stimulus.

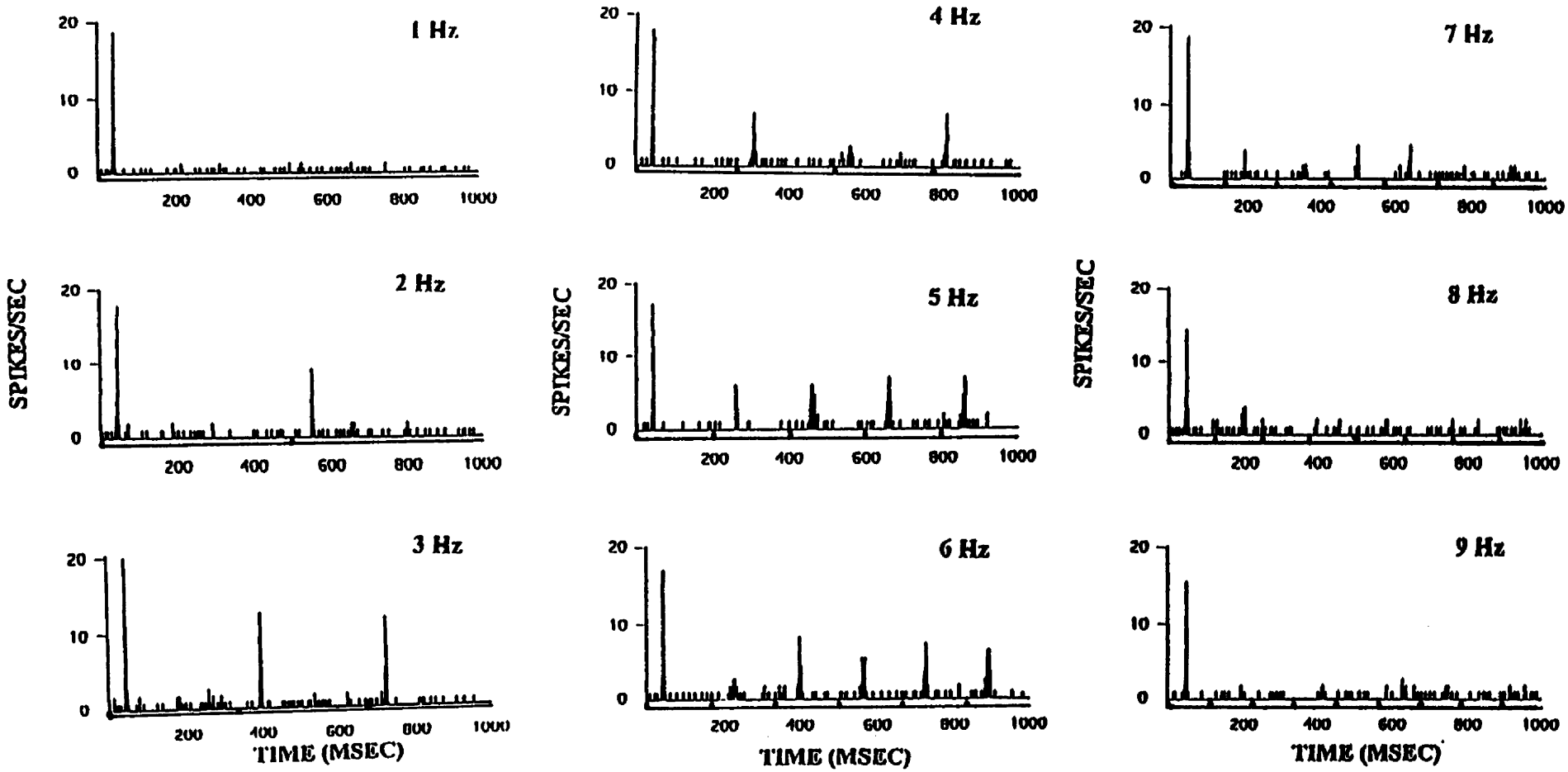

1 Hz
2 Hz
3 Hz
4 Hz
5 Hz
6 Hz
7 Hz
8 Hz
9 Hz
SPIKES/SEC
SPIKES/SEC
SPIKES/SEC
20
10
0
200
400
600
800
1000
TIME (MSEC)
TIME (MSEC)
TIME (MSEC)

Figure 4b

The distribution of the fundamental of the cell in part a, as a function of stimulus frequency. The linear regression (solid line) and exponential fit (dashed line) are included. The linear regression of the power at the stimulus fundamental frequency determined that the CFF threshold of this cell was 8 Hz.

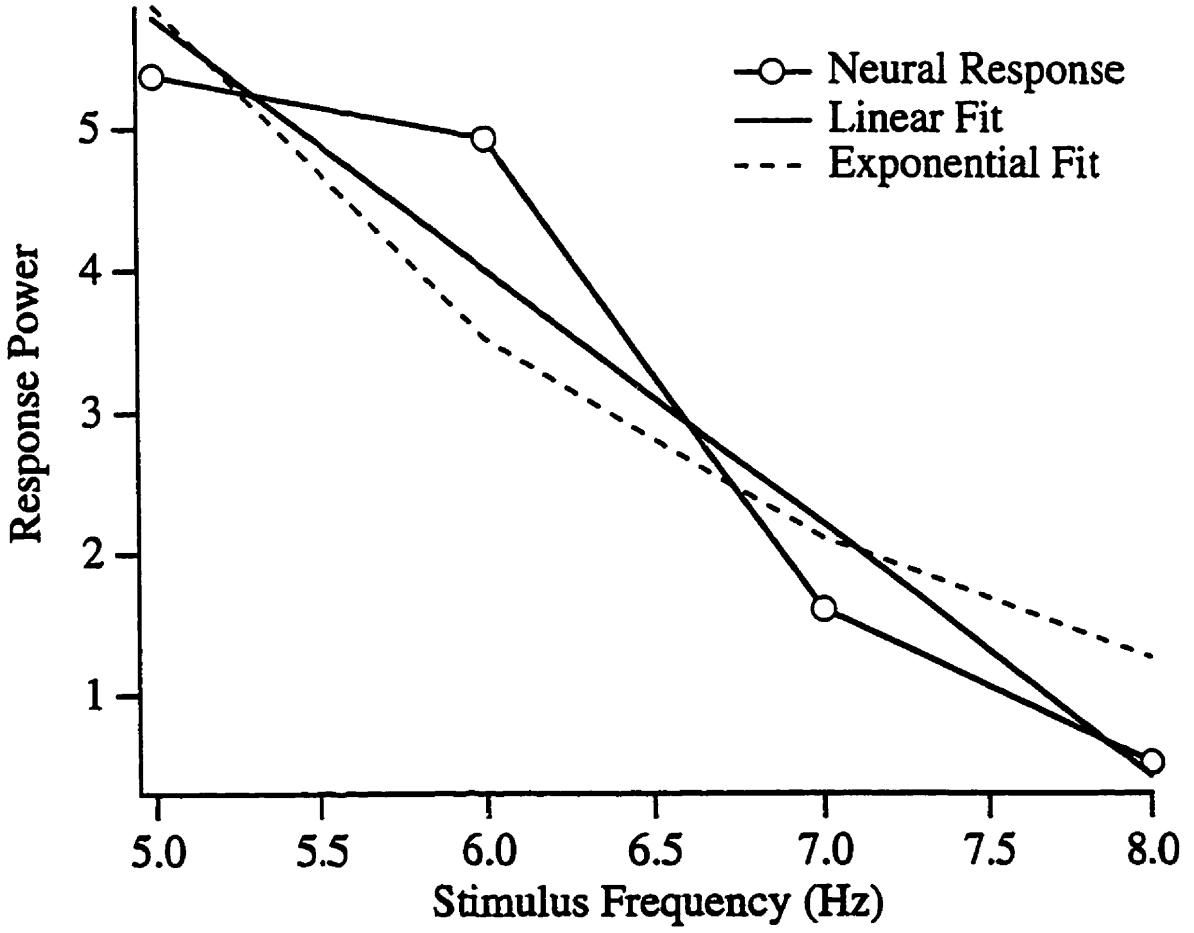

Neural Response
Linear Fit
Exponential Fit
Response Power
1
2
3
4
5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
Stimulus Frequency (Hz)

Figure 5a

A series of PSTHs indicating the response of a hypercomplex cell recorded from the primary visual cortex of an old animal. Time of stimulus presentation (1000 msec), divided into 200 bins of 5 msec, is displayed on the x-axis. Squares below the histograms indicate the timing of the flashes. This cell was able to entrain to frequencies up to 12 Hz and although it appeared unable to entrain at 13 Hz, it was able to follow the first few flashes at 14 Hz. Above 14 Hz however, the cell was unable to entrain to each flash of light and responded primarily to the onset of stimulation.

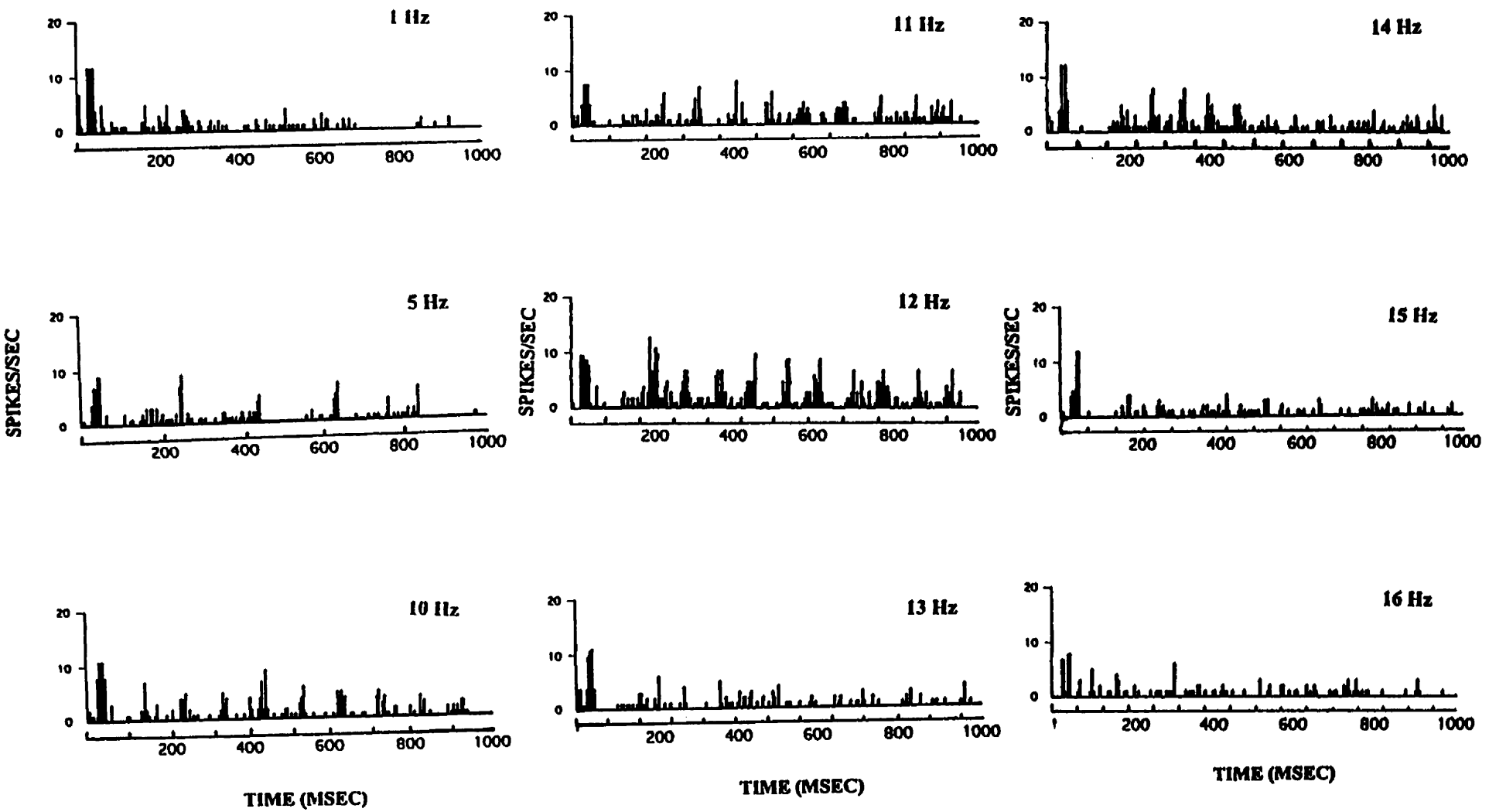

1 Hz
11 Hz
14 Hz
5 Hz
12 Hz
15 Hz
10 Hz
13 Hz
16 Hz
SPIKES/SEC
SPIKES/SEC
SPIKES/SEC
20
10
0
200
400
600
800
1000
TIME (MSEC)
TIME (MSEC)
TIME (MSEC)

Figure 5b

The FFT of the response of the cell in part a, confirmed that the CFF threshold for this cell was 14 Hz.

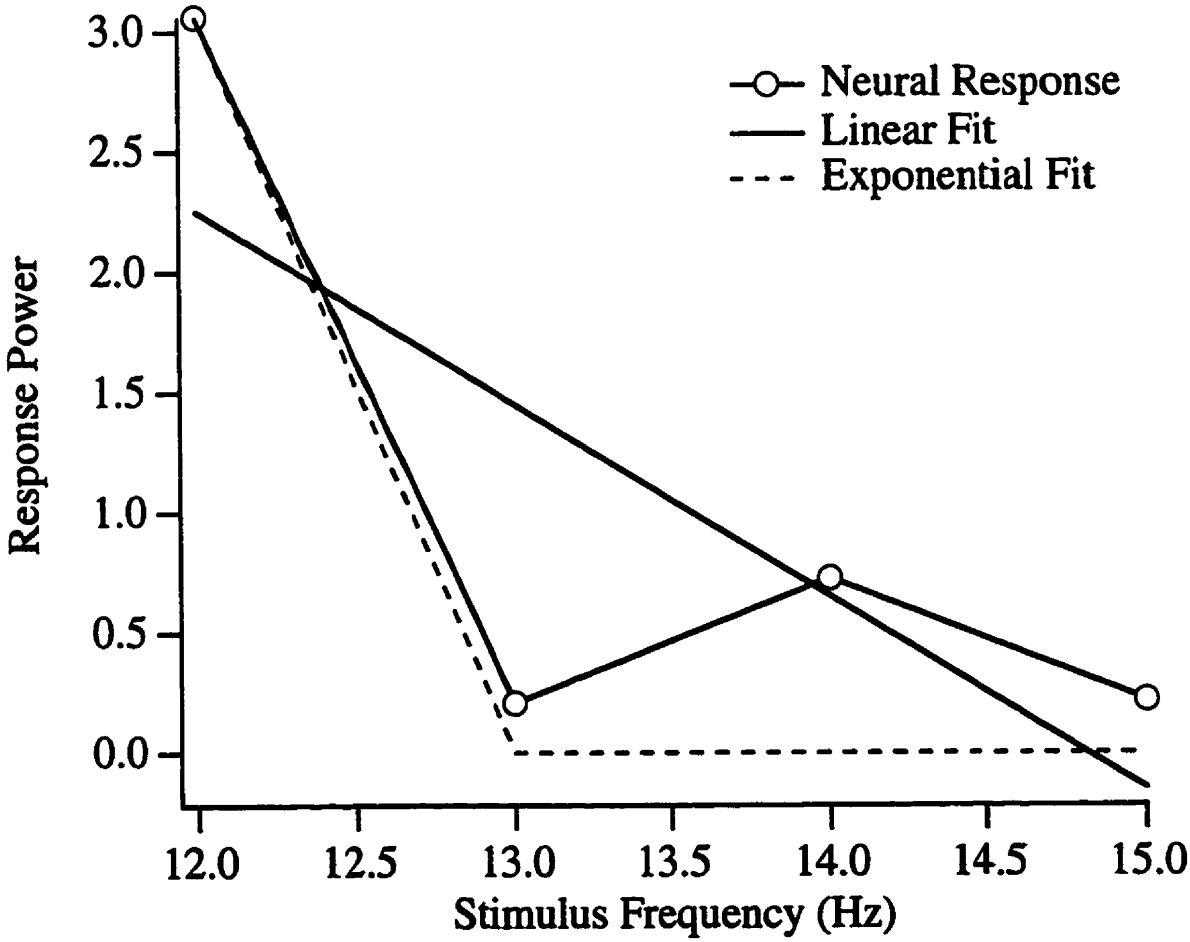

Neural Response
Linear Fit
Exponential Fit
Response Power
3.0
2.5
2.0
1.5
1.0
0.5
0.0
12.0
12.5
13.0
13.5
14.0
14.5
15.0
Stimulus Frequency (Hz)

Figure 6

The mean CFF threshold for old animals (11.89 ± 2.7 Hz) was significantly lower than the mean threshold for young animals (21.54 ± 6.0 Hz), $p < .001$. Error bars indicate standard error.

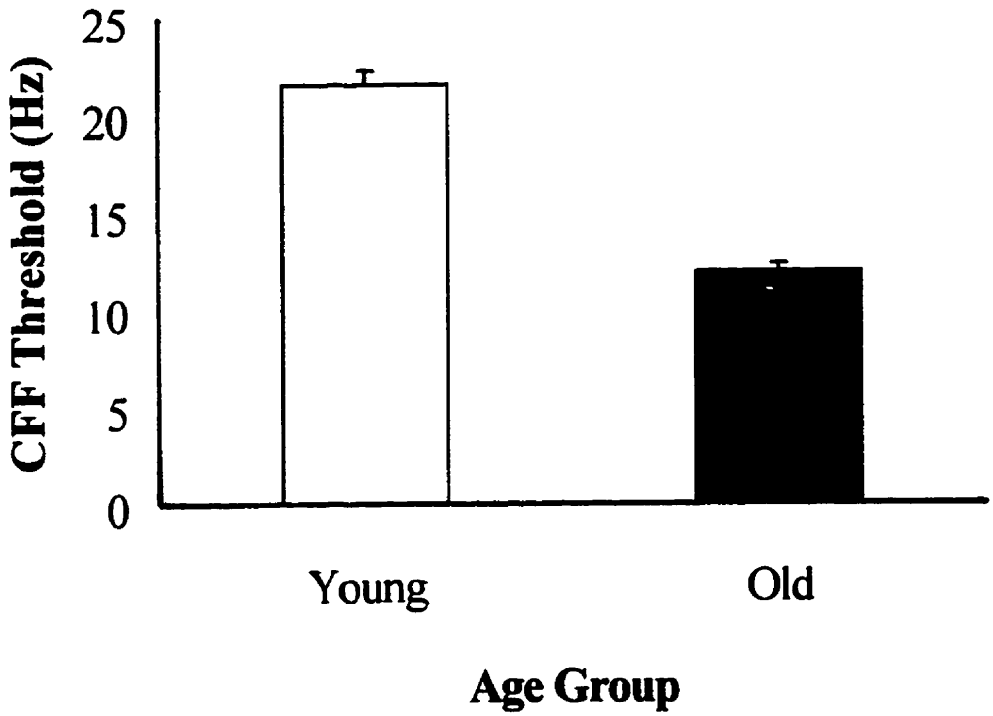

CFF Threshold (Hz)
25
20
15
10
5
0
Young
Old
Age Group

Figure 7

There was a significant difference in mean CFF threshold values recorded between simple, complex and hypercomplex cells in young animals, $p < .001$, however no such difference was found in old animals. Simple, complex, and hypercomplex cells recorded from the visual cortex of old subjects all show reduced CFF thresholds compared to young subjects. In both young and old subjects, simple cells demonstrated the lowest mean CFF threshold values. ANOVA indicated a significant interaction between age and receptive field classification for CFF threshold values, $F(2, 92) = 5.121$, $p < .05$. Error bars indicate standard error.

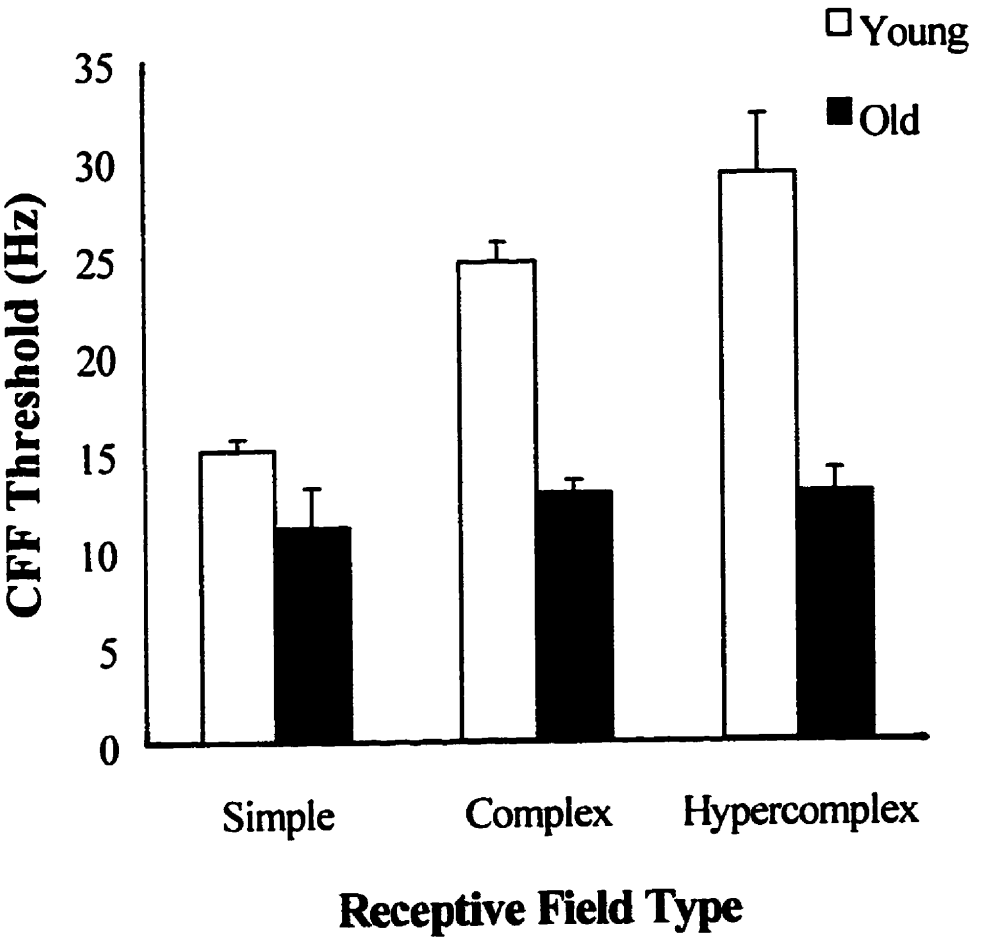
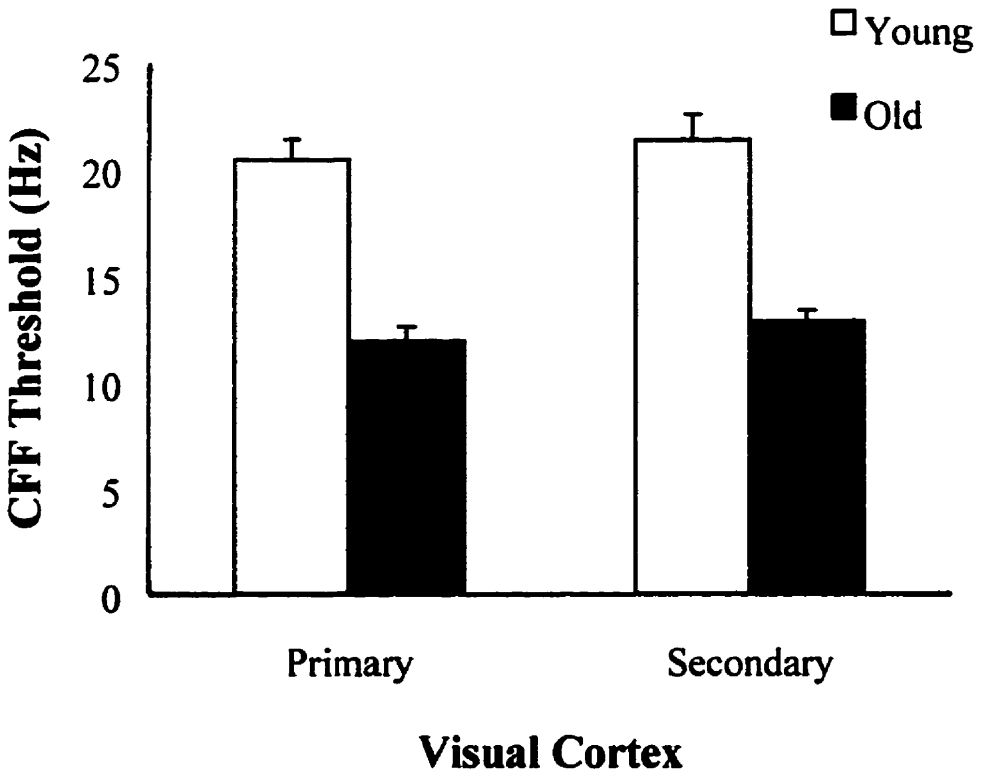

Young
Old
35
30
25
20
15
10
5
0
CFF Threshold (Hz)
Simple
Complex
Hypercomplex
Receptive Field Type

Figure 8

There was no significant difference between mean CFF thresholds recorded in primary and secondary visual cortex in either young or old animals, $p > .05$. However, ANOVA indicated that the age-associated decrease in CFF threshold values was highly significant in both primary and secondary visual cortex, $p < .001$. Error bars indicate standard error.


Young
Old
CFF Threshold (Hz)
25
20
15
10
5
0
Primary
Secondary
Visual Cortex

4.0 DISCUSSION

The current results of extracellular single cell recordings in the visual cortex of young and old Long Evans hooded rats, demonstrate a significant difference in the neural response to flicker stimulation in the two age groups. Physiological CFF thresholds in old animals were significantly lower than CFF thresholds in young animals. Age-associated reductions in CFF thresholds were observed in both primary and secondary visual cortex and across all types of cells recorded. These results support the hypothesis that temporal processing is reduced in the senescent visual system, and demonstrate that differences in cortical neuronal responding may underlie visual temporal processing deficits observed in the elderly.

4.1 Response characteristics

Single cells in the visual cortex of both young and old rats have similar response characteristics that enable them to encode flicker and contribute to the perception of flicker fusion. At low frequency flicker stimulation single cells were able to entrain to the stimulus, displaying a discrete response to each flash of light. However, once a certain high frequency of flicker stimulation was reached, cells were unable to follow each flash and responded instead as if the stimulus were a continuous or fused light. After CFF threshold was reached, the majority of cells in both age groups responded only to the onset of the stimulus, similar to the "ON" response recorded to a presentation of a bar of light within the receptive field. These cells thus signaled the onset of a light source. In comparison, few cells in either age group responded to both the onset and offset of the light, and cells responding to the offset of stimulation were recorded only in young animals. The absence of this response in old animals may be a result of random sampling due to the small number of these cells, or may reflect a deficit in the ability of the senescent visual system to detect target offsets (Kline et al., 1990).

Although comparisons between physiology and behaviour must be made with caution, the differential responding of single cells at certain frequencies of flicker implicates a physiological mechanism in the visual cortex corresponding to the behaviorally observed perception of flicker and fusion.

4.1.1 Response to CFF in the young visual system: The average CFF threshold across all neurons recorded in young subjects was 21.5 Hz. Cells were recorded that responded preferentially to low frequency flicker stimulation while others were able to respond to higher frequencies of flicker, thus a wide range of CFF thresholds from 10 to 35 Hz was recorded across individual subjects. Tardif, Bergeron, Lepore and Guillemot (1996) reported that single cells in cat visual cortex (areas 21a and 18) similarly display broad temporal frequency tuning as they responded to a wide range of drifting sine wave gratings between 0.5 and 24 Hz. These results suggest that single cells in the visual cortex process specific frequencies, that when taken together, encompass the total range of possible frequencies. Considering the diverse temporal processing demands of an animal's environment, it is probable that cells able to encode both low and high temporal frequencies exist.

No other studies have examined physiological CFF thresholds in the rat, however Williams et al. (1985) reported that the behavioural CFF threshold of albino rats was 35 Hz when luminance was 0.7 log (ft-L). Although the current average neural CFF in young subjects is somewhat lower than this behaviorally derived threshold, the upper limit to CFF thresholds observed physiologically at the same luminance is in accordance with behavioral thresholds. The range of neuronal CFF thresholds may reflect individual variation in behavioural CFF, although it is possible that sampling bias due to the small number of cells recorded in each subject could influence the average CFF in individuals.

4.1.2 Response to CFF in the aged visual system: In comparison to CFF thresholds in young animals, there was a reduction in both the minimum and maximum CFF thresholds in old animals and the range was reduced to between 6 and 15 Hz. An overlap of cells was therefore recorded in young and old animals responding to frequencies between 10 and 15 Hz. The reduction in both the minimum and maximum CFF thresholds indicates that during aging, neurons lose their sensitivity to a wide range of temporal frequencies as well as a specific response to high temporal frequencies (Spear, 1993). The deficit encoding high flicker frequencies indicates an age-associated reduction in high frequency temporal resolution (Kline & Schieber, 1982).

The reduction in physiological CFF values may underlie the behavioural observations of reduced CFF and temporal resolution in the aged human visual system (Brozek and Keys, 1945; Misiak, 1947; Cronin-Golomb, Corkin, Rizzo, Cohen, Growdon & Banks, 1991; Lachenmyer et al., 1994). Due to the different life spans and visual capabilities of rats and humans, it is inappropriate to compare absolute CFF values. One way to discount the differential life spans is to compare the CFF ratio of young to old. The present study yields a ratio of 1.81, which is fairly similar to the ratio obtained by Misiak (1947) of 1.23 from young (19 – 30 years) and old (63 – 87 years) human observers. However, even ratios may not be truly comparable due to physiological versus behavioral measures.

4.2 Receptive field properties and CFF

The range of CFF thresholds observed in the present study can partly be accounted for by the differential response characteristics of certain types of cells in the visual cortex. Simple cells encoded lower threshold values than either complex or hypercomplex cells in both age groups. This is consistent with reports that simple cells prefer slow velocities of movement

compared to complex cells which in the rat, can respond to stimulus speeds of 100°/sec (Parnavelas et al., 1981). The difference between age groups was that significant differences between the average CFF thresholds of simple, complex and hypercomplex cells were found in young, but not old, animals. Although fewer cells were recorded in old subjects, the results suggest a greater age-related reduction in CFF in complex and hypercomplex cells. This is an important finding because no other studies have described any effects of aging on the receptive field properties of single cells in the visual cortex. One study compared the center-surround receptive field organization in the dLGN of young (5 - 16) and old (25 - 28 years) rhesus monkeys but found no difference in response properties (Spear et al., 1994). Considering the similar classification of receptive field properties in cat (Hubel & Wiesel, 1962), monkey (Hubel & Wiesel, 1968) and rat (Parnavelas et al., 1983), the effects of age on the functional properties of neurons may indicate similar deficits in basic visual processing across species.

The present study found 77% complex, 15% simple, and 8% hypercomplex cells in the young age group. In the primary visual cortex (area 17) of Long Evans rats, Parnavelas et al. (1981, 1983) reported a distribution of 44% complex, 27% simple, 13% hypercomplex and 16% non-oriented cells. Because the present study did not include the classification of non-oriented (cells not displaying a discrete orientation preference otherwise responded as complex and were therefore classified as complex) it is difficult to directly compare these results. It is possible that the small number of simple cells encoding low frequencies of flicker in the current study may have biased the sample towards higher average values of CFF. However, the trend that complex cells are most numerous with few simple and hypercomplex cells in both young and old animals is comparable to previous results in the rat (Parnavelas, 1981), mouse (Drager, 1975), cat area 21a (Tardif et al., 1996) and monkey (Hubel & Wiesel, 1968).

4.3 Anatomy of the rat and CFF

Although temporal processing may be considered a function of receptive field type, it does not appear to map onto anatomical subdivisions within the rat visual cortex. A slightly wider range of CFF thresholds was recorded across secondary (14 – 35 Hz), compared with primary (15 - 31 Hz), visual cortex. Similarly, Tardif et al. (1996) reported that in the cat, area 21a neurons responded to a wide range of temporally modulated sine-wave gratings that was relatively higher than that in primary visual cortex. However, the differences between average CFF recorded in primary and secondary cortex in the present study were not significant in either age group, suggesting that information integration and processing over the entire visual cortex contributes to the perception of flicker and fusion.

4.3.1 Thalamocortical and tectocortical input: The integration required for the perception of flicker and fusion across anatomically distinct visual areas could be accomplished by input from both the thalamocortical and tectocortical pathways. The thalamocortical pathway transfers information from the retina through the visual dorsal thalamic nuclei and distinct visual thalamic reticular nuclei regions (Coleman & Mitrofanis 1996; Lozsadi, et al., 1996) to distinct lamina in both primary and secondary visual cortex (Bourassa & Deschenes, 1995). Extensive reciprocal cortico-cortical and subcortical connections in the rat (Thomas & Espinoza 1987; Shao & Burkhalter 1996; McDonald & Mascagni, 1996) could support the similar distribution of frequencies encoded throughout the visual cortex. In the rat, retinal ganglion cells also provide input to the tectocortical pathway which transfers visual information through the superior colliculus to secondary visual cortex (Dean, 1981). Temporal information is processed by both pathways in other species, for example, monkey area MT and cat area 18, which contribute to the analysis of motion, receive

direct input from the superior colliculus as well as the LGN (Wall, Symonds & Kaas, 1982; Spear, 1993). Movement over a wide range of velocities is encoded by cells in both the dLGN (Montero & Brugge, 1969) and superior colliculus (Dean, 1990), implicating both pathways in the processing of temporal information. The tectocortical and thalamocortical pathways may combine to support the perception of transient stimuli, including flicker. Although it is clear that the rat visual cortex is anatomically heterogeneous (Espinoza & Thomas, 1983), it appears that the existence of separate visual representations may not provide an anatomical base for the differential processing of temporal information in the rat. However, it is possible that detailed mapping studies may elucidate more specific patterns of CFF processing.

4.3.2 Population versus single cell coding: A common analysis of information processing in the visual cortex involves mapping specific visual functions onto discrete anatomical subdivisions (Zeki, 1993). However, the inability of studies to consistently demonstrate distinct functional differences between cortical areas, indicates that striate and extrastriate cortical areas and single neurons may instead be multifunctional, and participate in parallel, integrated processing (Schiller, 1996; Gegenfurtner & Hawken, 1996). The observation that primary and secondary visual cortex process a similar range of CFF thresholds lends support for this generalist view of information processing, or a population code, within the visual cortex. A population code assumes that information is represented across an entire array of cells (Milgram, 1998). Evidence for a population code is also found in the observation that single cells within an individual subject displayed little variability in their CFF thresholds. However, there is also evidence for single cell coding for CFF. In some animals, a much wider range of CFF thresholds were recorded, which included the highest threshold recorded physiologically of 35 Hz. This is in accordance with a behavioural CFF of 35 Hz in the rat

(Williams et al., 1985) and indicates that the highest rate of flicker processed physiologically may contribute to the behavioral perception of fusion, and not the average threshold. The fact that evidence for population and single cell coding exists, suggest that a population code may account for the average CFF in separate visual cortical areas, but that a single cell code processing the highest rates of flicker produce the strongest signal that contributes toward perception.

To distinguish between these two types of coding, it would be necessary to reduce the bias produced by unequal sampling by recording a greater number of cells per animal that is equal across all subjects. Another method would be to combine physiological and psychophysical techniques. Salzman and Newsome (1994) combined these two techniques to determine how rhesus monkeys discriminated among various directions of motion. They presented motion visually and generated a signal for a different direction of motion by electrically stimulating neurons in visual area MT that encode specific directions. They found that the monkeys did not choose a direction that was an average of the two signals but chose the direction encoded by the largest signal in the representation of motion direction, a "winner-take-all" decision process.

Predictions of CFF can be made based on the method of coding used by the cortex to achieve a perceptual discrimination of flicker and fusion. If a single cell code that responded to the highest frequencies of flicker processed physiologically provided a stronger signal for the behavioural perception of fusion, then the highest frequency encoded physiologically of 35 Hz accounts for behavioural observations of 35 Hz for CFF in the rat (Williams et al., 1985). A single cell code would then predict that the behavioral CFF of old rats would correspond to the highest frequency of flicker processed physiologically of 15 Hz. If however, a population

code was predominant, then the average CFF recorded physiologically in an individual may correspond to that individual's behavioural CFF.

4.4 Slowing in the aged visual system

Although no differences in CFF thresholds were found between the visual cortical areas of both young and old subjects, an age-associated decline in physiological CFF was observed in both primary and secondary visual cortex. Aging has commonly been thought to produce a general slowing of information processing mechanisms (Eriksen et al., 1970). A slowing down in temporal processing speed at the cortical level could also explain some of the deficits other than CFF reported by elderly individuals in apparently excellent optical health (Birren, 1979; Kline, 1987). For example, some older observers require longer stimulus durations to locate stimuli in their peripheral vision, indicating a relatively slower speed of visual processing (Ball, Owsley, Sloane, Roenker & Bruni, 1993). As well, impairment of higher order visual temporal processing is thought to underlie visual search or target localization problems in older patients (59-88 years) with normal or near normal visual fields (Owsley, Ball & Keeton, 1995). Behavioural observations of visual decline, including CFF, do support the suggestion of a slowing in visual processing speed in later life (Salthouse, 1990).

Slowing and the subsequent inability of aged cortical neurons to follow high frequencies of flicker could reflect the age-associated transient/sustained shift in visual processing proposed by Kline and Schieber (1982). They suggested that aging selectively affects the transient pathway which mediates visibility of low spatial and high temporal frequencies, features inherent to fast-moving stimuli (Spear, 1993). Loss of transient channels responding to high frequencies could account for the changes observed in older individuals,

including the protracted persistence of neural effects following visual stimulation (Kline, 1987) and inability to detect target offsets (Kline et al., 1990). The stimulus persistence model attributed differences with age in temporal resolution to a lag in the recovery of individual neurons following transient stimulation, such as a flash of light (Kline & Orme-Rogers, 1987). Increased persistence of stimuli in the senescent nervous system would interfere with the neuron's response to subsequent stimuli, including flicker. However, no difference in mean high temporal frequency cutoff was found between magnocellular and parvocellular neurons in the dLGN of young and old rhesus monkey (Spear et al., 1994), suggesting that age-related changes in these two pathways exert an effect further up the visual system in cortical areas. The current study indicates that age-associated changes in neural temporal processing are apparent at the level of the visual cortex in the rat. This also supports previous studies indicating that fusion is determined by neuronal processing in the cortex of humans (Simonsen & Brozek, 1952; Kline, et al., 1990), monkey (Mishkin & Weiskrantz, 1959) cat (Schwartz & Cheney, 1966) and rat (Williams et al., 1985).

4.5 Neurobiological basis of normal aging

It is unlikely that a single anatomical mechanism could account for deficits in temporal processing with age and considerable controversy surrounds the neurobiological basis of normal aging. This is partly due to the inherent variability of aging both within and between individuals and across species (Selkoe, 1993). However, there are a few structural and functional changes that may contribute towards age-related visual deficits. Although an age-related decrease in neuronal density has been demonstrated in rats (Satorre et al., 1985), mice (Jucker & Ingram, 1997), monkey (Peters et al., 1997) and humans (Pakkenberg & Gundersen, 1997), it is no longer considered to be due to neocortical neuronal loss. The stability of

cortical neurons corresponds to a non significant loss of retinal ganglion cells with age (Kim et al. 1996), no decrease in cortical thickness, surface area or appearance of cell bodies in 35 year old rhesus monkeys (Peters et al., 1997). Consistent age-related changes in both rat (Cha, Lee, Park & Baik, 1997) and monkey (Moss, 1998) include a decline in metabolic rate and degeneration in cortical layer 1, which is probably due to loss of input from brain stem nuclei. In comparison, changes to neuroglia with age include accumulation of inclusions within all cell bodies (Peters et al., 1997) and an increase in glial cell number and density (Satorre et al., 1985; Ivy, McLeod, Petit & Markus, 1992).

4.5.1 Morphological aging of the cortex: Age-related changes in dendritic and synaptic structure and neurochemistry may contribute to some of the deficits observed in the senescent visual system. In rats, mice and humans, compensatory dendritic proliferation is observed with age, which is followed by regression in very old age (Connor, Diamond, Connor & Johnson, 1981; Selkoe, 1993; Jucker & Ingram, 1997). The pyramidal cells in occipital cortex layer III which are involved in cortico-cortical processing of information, are most susceptible to dendritic deterioration (Ivy, et al., 1992). In humans and rats, synaptic loss is the major correlate of age-related functional changes (Rakic, 1991; Jucker & Ingram, 1997). Impaired synaptic potentiation following repetitive stimulation in the hippocampus of aged (25 – 27 month) Fisher rats has been proposed to account for retention performance deficits in tests of memory in the same animals (Landfield, McGaugh & Lynch, 1978). In primary visual cortex, the density of synapses has been shown to decrease in 20 year old rhesus monkeys (Rakic, 1991) and 21 month Long Evans rats (Connor, et al., 1981).

Studies have also examined neurochemical changes that accompany aging, and in the aged rat occipital cortex there is a decrease in cells containing the neuropeptides, vasoactive

intestinal polypeptide and neuropeptide Y (Cha et al., 1997). These neuropeptides sustain CNS functioning and while the functional significance of this loss is unknown, it may interfere with the speed of temporal processing. An alteration in information processing could also result from a decrease in dopamine and serotonin turnover in the aged rat visual cortex (Herrera, Machado & Cano, 1993). Unfortunately there are discrepancies in the literature regarding the amount of change and any functional significance.

4.5.2 Age-related loss of white matter: Another age-related anatomical change that could contribute to the reduced ability of neurons in the visual cortex to entrain to high frequency stimulation, is a loss of white matter. Volumetric studies of magnetic resonance imaging (MRI) scans have revealed a statistically significant age-related loss of white, but not gray, matter in elderly (20-35 years) as opposed to young (5-14 years) rhesus monkeys (Moss, 1998). Double, Halliday, Kril, Harasty, Cullen, Brooks, Creasey and Broe (1996) confirmed that the small decline in cerebral volume loss in 46 to 92 year old humans was only within white matter. A significant and positive correlation has been found between white matter volumetric loss on MRI and extent of overall cognitive impairment (Moss, 1998). Since gray matter is preserved, loss of white matter cannot be attributed to a loss of axons but suggests that non neuronal cells, in particular the myelinating oligondendroglia, may be vulnerable to age-related changes (Moss, 1998). A decline in myelin could produce the age-related reduction in conduction velocities reported in both rat and human (Celesia & Daly, 1977; Contestabile, Suppressa, Tonelli, Giorgi, Antonnicola & D'Alba, 1995). A decline in conduction velocity could result in a slowing in transmission rate, overall cognitive slowing with age (Salthouse, 1990; Pakkenberg & Gundersen, 1997) and interfere with the encoding of high temporal frequency stimulation.

4.6 Reducing other possibilities

Aging in the visual system is a highly complex process that displays considerable individual variation (Sekuler & Sekuler, 1992). It is likely that the behavioral effects observed in an aging visual system are due to a combination of many processes, as opposed to a single process. The results of the present study implicate the involvement of the visual cortex in age-related deficits in perceiving flicker and fusion, however, the influence of subcortical structures cannot be entirely ruled out. Schwartz and Clark (1957) reported that the albino rat continues to discriminate between flicker at a frequency of 12 Hz and a steady light after removal of the visual cortex. However, the fact that high frequency discrimination is abolished after lesions of the visual cortex, indicates the critical role of the visual cortex in at least high frequency flicker discrimination. In the cat, Norton and Clark (1963) attributed impairment of flicker discrimination to the combined removal of visual cortex and superior colliculus, rather than to visual cortex alone.

It is also unlikely that age-related changes in the optics of the eye could alone account for the present results. Only those animals in excellent optical health were used, and the use of a high intensity light stimulus should have compensated for any elevated threshold of light required by the aging ocular media. The observation that light-induced retinal damage has been shown to reduce, but not abolish, CFF in the albino rat implicates higher order mechanisms for CFF (Williams et al. 1985). In human studies, temporal processing is unaltered by manipulation of pupil size (Lachenmyer et al., 1994) or degraded acuity (Ball & Sekuler, 1986). The current study provides further support for the notion that changes in the ocular media explain little of the diminished temporal processing capacity of the senescent visual system and indicates that the cause in mostly neural in origin. The localization of CFF

processing in the visual cortex is in accordance with previous reports indicating that temporal frequency is processed in the cortex (Walker et al. 1943; Sekuler, 1991; Spear, 1993).

4.7 Applications in the real world

For these results to be significant to the elderly in everyday living, the experimental procedure needs to be indicative of real-life conditions. A common criticism of clinical tests of visual aging is that the stimuli are high in contrast, illumination and involve isolated, static targets which subsequently miss detecting many age-related visual deficits (Sekuler, 1991). Critical flicker has applications in cinematographic and television fields. As well, flicker can be experienced while driving on a heavily treed road whereby passing each tree causes an alternation of light and shadow to be cast upon the car's windshield (Woodruff & Neill, 1990). Under such conditions, the changing speed of the automobile will result in different frequencies of flicker to be processed rapidly by the driver. As noted in the introduction, vehicle accidents involving the elderly are associated with a deficit in the ability to accurately perceive changing speeds (Kline et al., 1992). A deficit in timing ability can not only have a direct effect on driving, but also on other functions that contribute to the visual problems of the elderly, such as visual attention (Ball et al., 1993). This indicates that not only must individual functions be examined separately, but the relationship between various aspects of aging must be determined to obtain a more complete assessment of the age-related visual deficits experienced by the elderly.

4.7.1 Research implications: This study describes the neurophysiological response to varying frequencies of flicker and thus contributes to our understanding of temporal processing in young and old visual cortex. While the objective was to determine the neural basis for age-related decreases in behavioural CFF thresholds in elderly humans, the results offer important

implications for both clinical and research applications. In research, the rat is commonly used to assess aging and memory, and before any results are attributed to memory impairments, it must be assured that the results are not due to a decline in sensory ability. An age-associated decline in temporal processing may have an effect on aspects of behaviour related to performance on memory tasks and analysis of temporal, as well as spatial acuity, is therefore critical.

4.7.2 Clinical implications: In clinical applications, adding tests of temporal processing to commonly administered tests of acuity in physician's office may help detect early pathology in the visual system (Castor & Carter, 1995). For instance, glaucoma damages the magnocellular pathway which mediates motion perception, and early glaucoma may be present despite tests indicating normal foveal function (Wood & Bullimore, 1995). An easily administered test such as CFF, which isolates temporal processing, may therefore help in the early detection of glaucoma.

Critical flicker can be used to assess temporal processing deficits in the senescent visual system, and may also lead to a novel therapeutic tool to help the elderly improve their temporal processing abilities. Ball and Sekuler (1986) demonstrated that although the ability to discriminate among two directions of moving random dot patterns declines in older observers, with practice both young (18 – 28 years) and old (62 – 72 years) observers were able to achieve lasting improvements in direction discrimination judgements. The results could not be attributed to differences in acuity, because when the acuity of young observers was degraded, the ability to distinguish between highly similar directions of motion was unimpaired. Although improvement was specific to the task, the success of such a simple training program suggests that plasticity in the aged cortex may allow for improved temporal

processing and CFF. At the anatomical level, plasticity, or an increase in complex dendritic arborization, in the aged rat cortex can be induced by exposure to visually stimulating environments (Selkoe, 1993). Retained plasticity in the visual cortex is likely possible through the stable concentration of noradrenaline, which plays an important role in the plasticity of the visual cortex (Herrera, et al., 1993). This study provides valuable information as to the neural basis of age-related reductions in CFF and insight into temporal processing, which is a critical aspect of vision. The results should be combined with research on spatial processing to develop a global understanding and assessment of aging in the visual system.

5.0 CONCLUSIONS

5.1 General Summary

Vision loss is one of the most common impairments among the elderly and can have profound implications for their well-being (Salvage, 1995) and everyday living (West, Munoz, Rubin, Schein, Bandeen-Roche, Zeger, German & Fried, 1997). One specific function that declines with age involves visual temporal processing, and the focus of the current study was to elucidate cortical changes that could underlie the slowing of information processing and subsequent decreased CFF thresholds observed in the elderly. The differential response of single cells in the visual cortex of young and old rats provides evidence for the involvement of central neural structures in the processing of flicker and fusion. This is consistent with research indicating that optical factors can only account for a small portion of age-related losses and that the retino-geniculate pathway is little affected by age (Spear, 1993; Sekuler, 1991; Kline et al., 1990). The similarities between receptive field types, and the division of distinct visual cortical areas in the rat and other species, suggests that findings regarding basic visual and age-related changes in temporal processing may reflect similar processing in higher

species, though extrapolation to the human system is made with caution. Although the results cannot discriminate among various neurobiological explanations of aging, a decrease in myelination of the visual pathways (Celesia & Daly, 1977; Moss, 1998) and subsequent reduction in conduction velocity may produce the temporal processing deficits underlying reductions in CFF with age. Elucidating the physiological mechanisms underlying the behavioral changes experienced in old age may prove critical for early detection of pathology and subsequent improvement for the life style of aging individuals, where visual functioning is critical to normal everyday living.

5.2 Directions for future studies

There are a number of directions that future studies could take to expand on the current results. Firstly, the inclusion of a young adult age group could help examine how changes in neuronal temporal processing occur throughout the aging process.

Second, our lab is currently conducting similar aging experiments with stimuli that move location over time, as conclusions are strengthened when a variety of experimental paradigms combine to produce similar effects. The combination of these results should increase our understanding of how speed and temporal information are integrated, and change, in the senescent visual system. A detailed mapping examination of columnar organization by speed and CFF could produce a more complete knowledge of temporal processing within both young and old aging visual system.

Finally, examination of behavioral measures of CFF and physiological measures in a within-subject design of CFF would isolate the variability inherent during the aging process. It would also allow the predictions based on population and single cell coding of temporal processing in the visual cortex to be tested.

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7.0: PUBLICATIONS AND POSTERS ARISING FROM THIS WORK

Mendelson, J. R. & Wells, E. F. (1998). The neurophysiological effects of aging on the ability of the visual system to process temporal information. Abstract and Summary in press. Brain and Cognition.

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APPENDIX A

Young Subjects	CFF	Receptive Field	Location	Response
P1.01	22	Complex		Off
P2.01	31	Complex		Off
P2.02	32	Hypercomplex		Random
P5.01	31	Complex		On
P5.02	32	Complex		On
P10.01	15			On
P11.02	29			On
P14.01	27			On
P14.02	19			On
P17.01	21			On
P18.01	17			Off
P18.02	17			On
P18.03	10			On and off
P18.04	16			On and off
1.01	35		Oc2L	Random
3.03	28		Oc2L	Random
5.03	24		Oc2L	On
5.04	19		Oc2L	Random
6.04c	20		Oc2L	Random
7.02	15		Oc1	On
7.02b	15		Oc1	On
7.02c	17		Oc1	On
7.03	15		Oc2ML	Random
7.03b	16		Oc2ML	Random
7.04	17		Oc1B	Random
7.04b	17		Oc1B	Random
7.04c	15		Oc1B	On
8.04	20		Oc1	On
8.06b	20		Oc2MM	On
8.07	19		Oc1	On
8.07c	19		Oc2MM	Random
9.01	24		Oc1B	On
9.02	16		Oc1B	On
9.05b	15		Oc2MM	Random
9.06	33		Oc2L	On
9.06b	20		Oc2L	Random
10.01	21		Oc1	On
10.03	27		Oc1M	On
10.04	34		Oc2L	On
10.06	31		Oc1B	On
11.03	14		Oc2L	Random
12.01	19		Oc2L	Random

13.01	21	Complex	Oc1	Random
13.02b	29	Complex	Oc2L	On
13.03	21		Oc2L	On
14.07	22	Complex	Oc1	On
15.01	18			On
15.05	19	Complex	Oc2L	On
15.06	17		Oc2L	On
15.07	22	Complex	Oc2L	On
15.07b	18	Complex	Oc2L	On
16.03	15		Oc1	On
16.03b	20	Complex	Oc1	On
16.05	22	Complex		On
16.05b	27	Complex		On
17.01	16	Simple	Oc1	On
17.02	25	Complex	Oc1	On
17.10	20	Complex	Oc2L	On
18.03	23	Complex	Oc1M	Random
19.01	22	Complex	Oc1B	On
19.02	25	Complex	Oc2ML	On
19.03	30	Complex	Oc1B	On
20.01	29			On
20.03	26	Hypercomplex	Oc1M	On
20.05	30	Complex	Oc2ML	On
21.05	16	Simple	Oc2L	Random
22.02	14	Simple	Oc2L	On
22.03	14	Simple	Oc2MM	On

APPENDIX B

Old Subjects	CFF	Receptive Field	Location	Response
P7.02	9			On
P7.03	8			On
P8.01	14			On
P8.02	15			On
P8.03	13			On
P1.02	9			On and Off
P1.02b	8			On and Off
P1.02c	9			On and Off
P1.06	8		Oc2L	On
P1.06b	8			On
P1.06c	7			On
1.01	14	Complex	Oc1	On
1.01b	15		Oc1	Random
1.07	15	Simple	Oc1	On
1.01R	14	Simple		On
1.02R	14	Complex	Oc2L	On
1.04R	15	Complex	Oc1	On
2.01	11	Hypercomplex	Oc1	Random
2.04	6	Complex	Oc1	On
2.07	12	Complex		On
2.11	11	Complex	Oc2L	On
2.11b	10		Oc2L	On
2.12	11		Oc2L	On
2.12b	15		Oc2L	On
2.13	15			On
3.02	12	Hypercomplex	Oc1M	On
3.03	14	Complex	Oc2L	On
3.01R	12	Complex	Oc1M	On
3.03R	8	Simple	Oc1	On
3.06R	9		Oc1	On
4.04	13		Oc1	On
4.08	7	Simple	Oc1	On
4.01R	14	Complex	Oc1	On
4.02R	11		Oc1	On
5.01	13	Complex	Oc2L	On
5.01b	11	Complex	Oc2L	Random
5.03	12		Oc1	Random
5.06	14		Oc2M	Random
5.07	14	Complex	Oc1M	On
5.08	15	Complex	Oc2L	On
5.09	14		Oc2L	On
5.09b	13		Oc2L	On
5.09c	14		Oc2L	Random
5.10	15	Hypercomplex	Oc2L	Random
5.11	14		Oc1	On