ADAPTATION OF RESPONSES TO PROLONGED STIMULATION IN SINGLE NEURONS IN AREA 17 OF THE CAT

by

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Abstract

The locus and mechanisms of adaptation of neurons in Area 17 of the cat were investigated with extracellular unit recording techniques. Following prolonged visual stimulation, the responses of cells in Area 17 were reduced. The adaptation-induced changes in the responsivity of neurons could be restricted to small regions of the cell's receptive field and could show adaptation effects which spread asymmetrically across the receptive field. Prolonged unidirectional motion resulted in changes in the excitatory and inhibitory interactions between receptive field positions. These changes are thought to underlie the adaptation-induced changes in direction selectivity in cortical cells. The adaptation was not reduced by pharmacological agents which block the inhibitory neurotransmitter gamma-aminobutyric acid. Neurons in the lateral geniculate nucleus did not show adaptation at rates of stimulation which were optimal for inducing adaptation in cortical neurons. These experiments demonstrate that the adaptation of responses observed in visual cortical cells is not due to a general process which affects the responsivity of the cell, nor is adaptation the product of a GABAergic inhibitory input onto the cell. Rather adaptation must be a process occurring locally in either the pre or postsynaptic terminal or distal dendrites.
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Foreword

A portion of this thesis has previously been published as a full length paper 1 or as conference proceedings 2,3,4. In each case all the data was collected and the papers written by the Thesis author while the Second Author provided the software essential for data collection and played an editorial role. The Senior Author (the students supervisor) provided the funds and equipment for the experiments and helped develop the experiments and edit the papers.


We agree that the above statements are true.

Stuart Graham Marlin

Robert M. Douglas

Max S. Cynader
We experience adaptation effects every day and are usually unaware that this process is happening. For example, imagine arriving at work being overcome by the odor of a new perfume or cologne of a co-worker. The sensation is first overwhelming but within a short time you become completely unaware of the odor. Each sensory system has a mechanism for removing constant stimuli from our attention. The somatosensory and auditory systems have very rapid adaptation systems (ms to seconds) (Hill, Mo, & Stange, 1989; Kuno, 1983; Lasky & Yang, 1986; Lundstrom, 1986; Ronken, 1990; Shannon, 1983; Zelick & Narins, 1985) while in the visual system the adaptation happens over seconds or minutes. The differences in the time course of adaptation may reflect characteristics of the neuronal circuitry rather than different mechanisms. The present thesis examines the adaptation in visual cortex neurons and the results have implications for both the mechanisms of adaptation and the circuitry of the cortex.

decrement to repeated stimulation. It is the period of rapid change between between two steady states and its function is to allow the organism, organ or cell to perform more effectively in its immediate environment. Although in evolution adaptation requires a great deal of time (measured in generations), sensory adaptation occurs within a much shorter time frame of hours, minutes or seconds.

Sensory adaptation shares a number of properties with habituation which is a non-associative conditioning of a behavioral response. The terms "habituation" and "conditioning" have often been used to refer to sensory adaptation (Buchwald & Humphrey, 1962; Davies, 1976; Gibbs, Cohen, & Broyles, 1986; Saito & Fukada, 1986; Saul & Daniels, 1985) despite clear differences between these two processes. Habituation research began in the late nineteenth century and became popular with the early work of Pavlov, Thorndike and Watson (Buchwald & Humphrey, 1962). With the advent of visually evoked potential recording techniques habituation experiments were performed on the visual system. Hernández-Peón (1958) recorded evoked potentials from the optic tract, the lateral geniculate nucleus (LGN) and the striate cortex of the cat during presentation of hundreds or thousands of light flashed stimuli over a four hour period. They found that the evoked potentials were dramatically reduced in the visual cortex and the LGN. The decrements in visually evoked potential persisted for up to 24 hours but could be dishabituated by a novel stimulus (different in spatial or temporal frequency) in the awake and freely moving cat. A strong novel stimulus will usually result in a rapid dishabituation of the response to the previously habituated stimulus. This dishabituation is necessary for the habituation of a response to be referred to as non-associative learning but is rarely observed in sensory adaptation. In fact many adaptation aftereffects will persist for hours or days despite exposure to novel stimuli (Harris, 1965).

While the function of habituation is to inhibit behavioral responses to non-novel
events the function of sensory adaptation is not clearly understood. Ohzawa et al (1985; 1982) suggested that adaptation acts as a contrast gain-control mechanism which shifts the dynamic range of the response and leads to enhanced sensitivity around the adapting contrast and to increase the visual systems ability to detect a change perceptually in the visual field. If this is the case, then the functional roles of habituation and sensory adaptation are clearly different. While habituation serves to inhibit a particular response and does not result in facilitation at nearby or functionally related synapses (Goldberg & Lukowiak, 1984), sensory adaptation can result in facilitation to nonadapted stimuli (Bach, Greenlee, & Buhler, 1988; Bradley, Switkes, & DeValois, 1988; Coletta & Adams, 1986; Greenlee & Heitger, 1988; Klein & Stromeyer, 1980; Lorenceau, 1987; Marlin, Douglas, & Cynader, 1989; Marlin, Hasan. & Cynader, 1988; Ohzawa et al., 1985; Ohzawa et al., 1982; Petersen, Baker, & Allman, 1985; Saul & Cynader, 1989a; Sclar, Lennie, & DePriest, 1989; Swift & Smith, 1982).

Ohzawa et al. (1985; 1982) argue that the contrast level of the stimulus is the factor which determines the rate of contrast adaptation. Maddess et al. (1988) disagree and suggest that the initial firing rate determines the rate of adaptation. In their experiments they studied the relationship between ocular dominance, temporal frequency, direction selectivity and the adaptation of visual cortical cells. They found that a cortical cell with a very high evoked firing rate adapted faster than one with a lower firing rate and concluded that the effect of contrast is simply to determine the initial firing rate and only secondarily alter the adaptation effects. Although their experiments suggest that temporal frequency and direction of motion of visual stimuli determine the differential adaptation effects, other stimulus parameters could also affect the adaptation process by changing the response rate.

Sensory adaptation can be highly specific for the adapting stimulus. The time course of recovery from adaptation to one stimulus is not affected by the presentation of either similar or relatively different stimuli. It is the specificity of adaptation
aftereffects which has led to the formulation of theories of spatial frequency channels in the visual system. Frequency specific adaptation has been described electrophysiologically in auditory cells (Hill et al., 1989; Parkins, 1989; Phillips, 1985; Phillips, 1990; Phillips & Hall, 1987; Ronken, 1990; Shannon, 1983; Zelick & Narins, 1985) and somatosensory cells (Hollins, Goble, Whitser, & Tommerdahl, 1990; Homonoff & Martin, 1983). In the visual system a grating composed of alternating light and dark bars of a particular size is presented and after prolonged exposure the subject's contrast threshold to detect this stimulus is higher but the change in threshold is limited to a small range of spatial frequencies similar to those of the adapting grating (Bradley et al., 1988; Georgeson, 1988; Georgeson & Georgeson, 1987; Georgeson & Harris, 1984; Georgeson & Turner, 1985; Greenlee & Magnusson, 1987; Greenlee & Magnusson, 1988; Greenlee, Magnusson, & Nordby, 1988; Klein & Stromeyer, 1980; Lorenceau, 1987; Magnusson & Greenlee, 1985; Magnusson & Greenlee, 1986; Manahilov & Vassilev, 1986; Perizonious, Schill, Geiger, & Rohler, 1985; Stromeyer, Klein, Dawson, & Spillmann, 1982; Wright, 1982; Wright & Johnston, 1982). These experiments show the stimulus specificity of pattern adaptation and suggest that there are separate "channels" for stimuli of varying spatial scales.

The selective adaptation of specific features of stimuli provide a clue to the locus of the adaptation process. For example, the retina will adapt to changes in luminance (Cicerone & Hayhoe, 1990; Cicerone, Hayhoe, & MacLeod, 1990; Crognale & Jacobs, 1988; Fulton & Graves, 1980; Green, 1986; Harris, Calvert, & Snelgar, 1990; Kamermans, Van Dijk, Spekreijse, & Zwepfenning, 1989; Korth, Ilschner, & Sembrzitzki, 1986; Naarendorp, Denny, & Frumkes, 1988; Saito & Fukada, 1986; Shevell & Burroughs, 1988) while visual cortical cells have been shown to adapt to changes in contrast, motion, spatial frequency, and orientation selectivity (Albrecht, Farrar, & Hamilton, 1984; Dean, 1983; DeBruyn & Bonds, 1986; Hammond, Mouat, & Smith, 1988; Hammond et al., 1989; Kulikowski, Rao, & Vidyasagar, 1981; Marlin & Cynader, 1986; Marlin et al., 1989; Marlin, Hasan, & Cynader, 1987; Marlin et al.,
Motion, spatial frequency and orientation selectivity are not present to a great degree in either the retina or the LGN. Many visual cortical neurons receive afferent inputs from pathways originating in the two eyes and are selective for binocular processing (binocular facilitation) and stereopsis (an offset in the image positions on each retina which allow depth perception in the visual cortex). Because the visual cortex possesses binocular cells and the LGN does not, it is easy to determine the cortical locus of the adaptation for these features. The argument is as follows: If the adaptation of spatial frequency channels, for example, resulted from a peripheral process (as in color aftereffects) and was only reflected in the visual cortex, then the adaptation would not show interocular transfer. If, however, prolonged monocular stimulation with a grating reduces the contrast sensitivity to that grating when tested through the adapted and the non-adapted eye, then the adaptation process must be occurring where binocular processing exists and this eliminates the retina and LGN.

Interocular transfer of adaptation has been shown for spatial frequency, motion, and orientation both psychophysically (Greenlee et al., 1988; Mitchell, Reardon, & Muir, 1975; O'Shea & Crassini, 1981; Paradiso et al., 1989; Selby & Woodhouse, 1981; Smith, 1983; Tyler & Nakayama, 1980; Wilcox, Timney, & St. John, 1990) and physiologically (Hammond & Mouat, 1988; Maffei, Bernardi, & Bisti, 1986). However, psychophysically, interocular transfer is not 100% in each of these feature detection systems. In motion processing the transfer is only about 25-50% which still leaves the possibility that a part of the adaptation effects observed originates either in the periphery, in monocular cells in the cortex, or at the terminals of geniculate fibers in layer 4 of the cortex (O'Shea & Crassini, 1981; Wilcox et al., 1990). Although the LGN demonstrates adaptation to sustained stimulus presentations, it does not show much adaptation to repeated transient flashed stimuli or moving sinusoidal gratings. LGN cells will continue to
fire action potentials when a light stimulus is flashed at a rate of up to 50 Hz without any visible decline in responsivity over time (Jones & Berkley, 1983). If the adaptation of cortical neurons is not a result of decreased responsivity of the cells in the retina or LGN then the question is: At what level do cortical cells adapt. If the adaptation is a general process which reduces the cells ability to fire action potentials then the decline in responsivity would be visible regardless of the stimulus used? However this is not the case. Cortical cells show adaptation effects which can be highly specific for spatial frequency orientation and direction of motion. These feature detection systems rely on extensive intracortical connections which themselves may be subject to the adaptation effects.

A significant debate has erupted within recent years as to the mechanisms underlying the adaptation of visual cortical neurons. A neuronal fatigue hypothesis was first proposed by (Wohlgemuth, 1911). He formulated a simple neuronal network which resulted in direction selective neurons and explained how prolonged unidirectional stimulation would fatigue certain components in the network thus explaining the psychophysical data on motion aftereffects. More recently, spatial frequency adaptation and orientation specific aftereffects have been explained using the same neuronal fatigue hypothesis (Blakemore & Campbell, 1969; Pantle & Sekuler, 1969). According to this model of adaptation, prolonged exposure to a stimulus of a particular spatial frequency reduced the firing rate of a small percentage of cortical neurons which were selectively sensitive to the stimulus parameters. Although not clearly, defined proponents of this neuronal fatigue hypothesis suggest that prolonged stimulation of visual cells results in a decrease in the firing of action potentials in those cells. The mechanisms by which that decrease occurs is not explained, however, a postsynaptic mechanism is implied. Recent research on the mechanisms of habituation in aplysia sensory-motor circuits suggests that a
presynaptic mechanism is more likely (Byrne, 1982; Castellucci & Kandel, 1974; Cawthorpe, Higgins, & Lukowiak, 1988; Gingrich & Byrne, 1985; Lukowiak & Peretz, 1980). It is generally agreed that with repeated stimulation (at the optimal temporal parameters for that circuit) the amount of transmitter released is reduced following habituation. This decrease in neurotransmitter release results from a depletion of the neurotransmitter in the presynaptic terminal or from a disruption of the mechanisms responsible for moving vesicles to the release site. It is highly likely that calcium-dependent potassium channels are involved in this presynaptic mechanism because the facilitation of transmitter release during sensitization or dishabituation is the result of a serotonin-induced blockage of the calcium-dependent potassium currents (Belardetti, Biondi, Brunelli, 1983; Boyle, Klein, Smith, & Kandel, 1984; Braha, Dale, Hochner, Klein, Abrams, & Kandel, 1990; Glanzman, Mackey, Hawkins, Dyke, Lloyd, & Kandel, 1989; Hammer, Cleary, & Byrne, 1989; Hawkins, 1989; Klein & Kandel, 1980; Ocorr, Tabata, & Byrne, 1986; Sacktor & Schwartz, 1990; Walsh & Byrne, 1989; Walters, Byrne, Carew, & Kandel, 1983). The habituation-induced changes in transmitter release could result from an intrinsic voltage-sensitive mechanism or from an extrinsic inhibitory input (Goldberg & Lukowiak, 1984).

It is also possible that in sensory adaptation there is an intrinsic mechanism within the postsynaptic cell which is activated by repeated stimulation and decreases the probability of the cell firing. Postsynaptic mechanisms include: receptor desensitization; an elevation of the membrane potential necessary for initiation of spikes and a progressive decrease in the EPSP by hyperpolarizing currents (K+ or Cl-).

A progressive increase in inhibition has also been suggested as a mechanism of sensory adaptation (Wilson, 1975). Wilson (1975) proposed an experience-dependent potentiation of inhibitory inputs onto cortical cells. He stated that a fatigue hypothesis did not account for the extremely long recovery times (up to 4 hours)
observed following adaptation times of up to 45 minutes because the magnitude of
the aftereffect saturates after a few minutes. Furthermore, it is possible to adapt
neurons which do not respond to the adapting stimulus (Maffei, Fiorentini, & Bisti, 1973).
Wilson's (1975) model applies a long-term potentiation (LTP) like co-stimulation
process involving inhibitory interneurons which provide feedback inhibition onto the
excitatory synapses. With repeated co-activation of the pre-synaptic and post-
synaptic processes, the strength of inhibitory synapse will be enhanced upon
subsequent afferent input. According to this model the excitatory synapses become
less effective due to the increasing inhibition uncoupling the presynaptic excitatory
input from the postsynaptic response. Repeated stimulation increases inhibition and
the probability of the postsynaptic cell firing a spike in response to the afferent fiber
releasing an excitatory transmitter becomes less and less until the two responses are
completely uncorrelated. With prolonged stimulation, the inhibitory synapses
become stronger while the excitatory synapses become weaker. Wilson assumes that
inhibitory inputs have a slightly larger spread across the cortex than the corresponding excitatory inputs such that adaptation at a single spatial frequency
would induce potentiation of the inhibitory inputs onto that channel as well as
neighboring spatial frequency channels.

Based on the behavior of striate cortical cells, Hubel and Wiesel (1962) formed a
hierarchical model for cortical feature analysis. In this model, the receptive fields of
simple cells were generated from aligned geniculate center-surround receptive fields.
Simple cells have at least two distinct subregions of their receptive field: an ON and
an OFF. A light stimulus flashed on within the ON region will result in spike
activity in the simple cell whereas a light stimulus flashed into an OFF region results
in inhibition of spike activity. The simple cells respond when a light stimulus is
removed from a receptive field OFF region. Complex cells have overlapped ON and
OFF regions such that the spatial location of the stimulus information is not important while the spatial frequency and direction of motion of the stimulus is. Hubel and Wiesel (1962) suggested that direction selectivity originated through linear summation of responses to a line moving from an OFF region to an ON region within the simple cell receptive field exciting the two subregions simultaneously (simple temporal summation). Movement in the opposite direction, from an ON area to an OFF area would not stimulate these two subregions simultaneously and so the response of the neuron would be much less. In their model, this simple cell direction selectivity was passed on up the hierarchical ladder to the complex and hypercomplex cells.

The visual cortex has been shown to be more similar to a parallel processing system and the assumption of linear interactions is true for only a minority of striate neurons (Ganz, 1984; Ganz & Felder, 1984; Movshon, Thompson, & Tolhurst, 1978a; Movshon, Thompson, & Tolhurst, 1978b). Furthermore, direction selectivity can be shown within a single simple cell subunit (Bishop, Goodwin, & Henry, 1974). Recent experiments have stressed the importance of specific non-linear interactions in the direction selectivity of cortical cells which may be mediated by special sequence-detecting subunits (Emerson, Citron, Vaughn, & Klein, 1987). These sequence detectors would include the proper temporal delay to allow for facilitation in the preferred direction and/or inhibition in the nonpreferred direction. In the 1970's Sillito began to explore the role of inhibitory neurotransmitters in response properties of single cells in the striate cortex (Sillito, 1977). Using the drug bicuculline, which is a blocker of the inhibitory neurotransmitter γ-amino-butyric acid (GABA), Sillito showed that direction selectivity in most simple cells was the result of inhibition of motion in the nonpreferred direction. He found evidence for a wave of inhibition extending 25' from the presence of a stationary edge, which would precede any edge travelling in the nonpreferred direction (Bishop et al., 1974). There also may be a wave of
facilitation which precedes an edge traveling in the preferred direction.

It is generally agreed that direction selectivity in complex cells is distinctly different from simple cell direction selectivity. In complex cells the direction selectivity is the same for dark bars and bright bars whereas the direction selectivity of simple cells can vary depending on the contrast of the stimulus (Goodwin, Henry, & Bishop, 1975). The invariant direction selectivity in complex cells may be the result of the completely overlapping ON and OFF receptive field subunits. Marlin, Hasan and Cynader (1988) have shown differences between simple and complex cells in the selectivity of adaptation. Simple cells displayed more direction selective adaptation than did complex cells. The direction selectivity of simple cells decreased following prolonged adaptation in the cell's preferred direction and increased following nonpreferred direction adaptation. In the population of complex cells examined, fewer cells displayed direction selectivity changes following prolonged unidirectional stimulation. The differences observed in this earlier work may result from the differential amounts of inhibitory and excitatory interactions within the receptive fields of simple and complex cells.

This thesis examines the effects of prolonged stimulation of the receptive fields of single cells in area 17 of the cat visual cortex. The aim of the thesis is to use the selectivity of the adaptation aftereffects to determine: 1. the locus of the adaptation within the geniculo-striate pathway and 2. the pre versus postsynaptic location of the adaptation mechanisms.

Part I of the thesis addresses the specificity of adaptation using a novel approach. Rather than adapt a cell with a moving stimulus of a particular velocity, orientation and spatial frequency, the cells were presented with an adapting stimulus restricted to a subregion of the cell's receptive field. Of particular interest is the spread of adaptation within the receptive field of simple and complex cells. The
questions that these experiments address are: 1) Will a cell show adaptation to such a small stimulus?; 2) Will adaptation at one position in the receptive field alter the response to stimulation in all receptive field positions? If not, will the adaptation effects be related to any known spatial parameters of the receptive field?; 3) Do ON and OFF regions in simple cells adapt equally and will prolonged stimulation of an ON region spread to neighboring OFF regions?; 4) Will adaptation effects spread equally in the cell's preferred and nonpreferred directions? The answers to these questions will tell us much about the intrinsic circuitry of the cortical cell's receptive field and whether cortical cells adapt via a general process which reduces the responsivity to all stimuli. If prolonged stimulation in a small region of the cell's receptive field resulted in a depression of activity at all receptive field positions, then this would suggest a general mechanism of adaptation which is tied to the response of the cell. However if adaptation effects are localized to the region of prolonged stimulation and are not related to any known spatial parameters of the cell, this would suggest that the adaptation effects are the result of synaptic depression or transmitter depletion in the presynaptic terminal (possibly depletion of transmitter in the LGN afferents). Chapter 3 describes more elaborate attempts to show adaptation in LGN afferent fibers recorded in the visual cortex and LGN cells recorded in the dorsal LGN. A bar stimulus was flashed in the receptive field of the LGN cell at the same temporal rate as used in the cortical cells. If the adaptation effects observed in the simple and complex cells result from decreased firing in the cells in the LGN then the same stimulus would produce noticeable adaptation of LGN cells. A second experiment addresses whether LGN cells can show more pronounced adaptation effects if the spatial and temporal frequency parameters are altered to better suit the known receptive field specificities of LGN units.

Part II of the thesis examines the stimulus specificity of adaptation using direction of motion as a variable during both adaptation and testing. Rather than
simply test the direction selectivity of the cell before and after prolonged unidirectional motion, the effects of prolonged unidirectional smooth motion on the responses to both smooth and apparent motion were examined. The amount of facilitation and inhibition was determined for motion in the preferred and nonpreferred directions by comparing sequences of flashes with single flash presentations both before and following adaptation. The questions which these experiments addressed were: 1) Would apparent motion stimuli display the same adaptation effects as smooth motion stimuli?; 2) Are there specific direction selective effects which are separate from general changes in responsivity?; 3) Would facilitatory and inhibitory interactions adapt differently when the adaptation stimulus is in the preferred or nonpreferred direction of motion?

Part III of the thesis deals specifically with the mechanisms of adaptation. Wilson's model of adaptation has become testable in recent years with the advent of pharmacological blocking agents for the inhibitory neurotransmitter GABA. Sillito iontophoretically applied bicuculline (a potent GABA-A antagonist) into small regions of the visual cortex while simultaneously recording the responses of single neurons. Sillito showed that direction selectivity in cortical neurons could be abolished with bicuculline and orientation tuning was reduced. More recently, DeBruyn and Bonds (1986) examined the effects of bicuculline on contrast adaptation to moving sine wave gratings. They argued that if Wilson's model was correct then blocking the GABA receptors in the visual cortex would block contrast adaptation. DeBruyn and Bonds (1986) found that although bicuculline increased the firing of cortical neurons, the rightward shift in the contrast response function (CRF) resulting from adaptation was identical to that observed without bicuculline. If anything the adaptation was more pronounced since some neurons with very low firing rates which did not display large contrast adaptation effects became more responsive with
bicuculline and the adaptation-induced shift in the CRF was more pronounced. Vidyasagar (1990) also examined the effects of bicuculline on pattern adaptation in visual cortical cells. He was interested in the relationship between postsynaptic firing rate and adaptation. He applied either bicuculline, GABA or glutamate to the cells to determine if neuronal fatigue accounted for pattern adaptation. His results supported those of DeBruyn and Bonds (1986); pattern adaptation was not blocked by bicuculline. Furthermore, if a response related fatigue was the mechanism of adaptation then strongly suppressing the cell's responses with GABA would prevent pattern adaptation and inducing postsynaptic responses with prolonged glutamate would induce adaptation. Application of GABA during repeated stimulation did not block the adaptation aftereffects in these cells. These experiments lead to the conclusion that neither a fatigue hypothesis nor Wilson's buildup of inhibition adequately explain the adaptation of cortical neurons. What is not evident in these experiments is the possible involvement of both GABA-A and GABA-B receptors.

Inhibition appears a particularly likely candidate for the mechanism of adaptation since GABA-B receptors can open slowly inactivating hyperpolarizing potassium channels (McCormick, 1989; McCormick & Williamson, 1989). The duration of the afterhyperpolarizing currents resulting from activation of these channels is in the order of seconds to tens of seconds (up to 60 seconds) and like other slowly inactivating $K^+$ channels they reduce bursting and are involved in spike frequency adaptation. In hippocampal pyramidal neurons the early and late slow afterhyperpolarization (sAHP) are responsible for long-term spike frequency adaptation. The sAHP appeared only after prolonged repetitive stimulation and is also $Ca^{2+}$ dependent (McCormick, 1989; McCormick & Prince, 1986; McCormick & Williamson, 1989; Schwindt, Spain, & Crill, 1989; Schwindt, Spain, Foehring, Chubb, & Crill, 1988a; Schwindt, Spain, Foehring, Stafstrom, Chubb, & Crill, 1988b). GABA-B receptors have been
shown to be present in the cat visual cortex (Bowery, Hudson, & Price, 1987; Shaw, Cameron, & Hendrickson, 1990; Shaw, Cameron, Prusky, Dyck, Cynader, & Hendrickson, 1989) while the sAHP has been demonstrated in pyramidal cells in rat visual cortex (Foehring, Schwindt, & Crill, 1989; Schwindt et al., 1989; Schwindt et al., 1988a; Schwindt et al., 1988b), human visual cortex (McCormick & Williamson, 1989) as well as other cortical and sub-cortical areas.

It is possible that a feedback inhibitory network which exists in the visual cortex, is the inhibitory mechanism of adaptation described in Wilson's model. Although GABA-A receptors have not as yet been shown to be involved in the adaptation of cortical neurons, it is possible that either GABA-A or GABA-B receptors may control visual cortical cell firing and may underlie pattern adaptation. Part III of the thesis addresses the activation of GABA-A and GABA-B receptors in the adaptation of cortical neurons.

Chapter 5 describes the effects of iontophoretic application of bicuculline (GABA-A antagonist) or phaclofen (GABA-B antagonist) on the adaptation of neurons in area 17. The normal responses of each cell to apparent motion stimuli described in Part II and the normal adaptation to prolonged preferred and nonpreferred direction stimulation were assessed. The effects of the GABAergic agents on the non-adapted apparent motion and smooth motion stimuli and the effects of prolonged unidirectional stimulation on these stimulus conditions were also assessed. Each trial run consisted of a pre-iontophoresis phase, an iontophoresis phase, and a number of post-iontophoresis recovery trials. At least 15 minutes separated repetitions of the entire sequence to allow for the GABAergic agent to dissipate and at least 1 minute separated adaptation trials to allow for recovery from adaptation. The questions addressed in Part III of the thesis are the following: 1) Would either bicuculline (GABA-A antagonist) or phaclofen (GABA-B antagonist) alone alter the time course of adaptation in visual cortical neurons?; 2) Were the
effects of bicuculline and phaclofen additive?; 3) Did either bicuculline or phaclofen reduce the direction selectivity of cells and if so was the adaptation under these different conditions direction selective?
Methods

Surgical Procedures and Physiologic Recording

Food deprived cats were anesthetized using i.v. Sodium Pentothal (2.5%) or Sodium Brietal (1.0 %) as required using a 23 or 25 gage butterfly-needle inserted into the forearm. Intravenous Atropine Sulphate (0.15 mg) or Atropine Methyl-Nitrate (0.125 mg) was administered to decrease salivation and to help prevent respiratory arrest during surgery. The butterfly-needle was taped into place and for the majority of animals all I.V. injections were through this route. In the last series of experiments (Part III) a venous cannula was inserted into the femoral vein halfway between the knee and ankle of the cat and the tube was fed up the vein for a distance of approximately 6 cm and tied in place with surgical suture thread. The wound was sutured with wound clips and could be examined periodically throughout the experiment. All subsequent surgical wounds were infused with 0.25% Bupivicaine Hydrochloride (Marcaine), a long lasting local anesthetic. A tracheostomy was performed to allow for artificial respiration during the experiments. A small incision was made between the larynx and the clavicle bone in the neck of the animal and the muscle covering the trachia was blunt dissected. The connective tissue and blood vessels surrounding the trachia were dissected away to the side and a 12 cm piece of suture (folded in half) was inserted under the trachia. The suture was cut into two 6 cm pieces which were placed at opposite ends of the incision. The trachia was cut partially and a human pediatric tracheostomy tube (size 3) was inserted into the trachia and tied in with the sutures already in place. The wound was sutured with wound clips and injected with 0.25% Bupivicaine Hydrochloride.

Following insertion of a tracheal cannula, the animal was placed in a stereotaxic apparatus which allowed unobstructed vision and clear hard contact lenses bathed in 3% saline were placed on the eyes to prevent corneal dehydration.
The animal's pupils were dilated using Atropine Sulphate (1%) and Phenylephrine Hydrochloride (10%) was administered topically to the eyes to retract the nictitating membrane. Marcain was liberally injected into the skin and muscle on the animals head. The skull was exposed by placing an incision the full length of the top of the head and blunt dissecting the muscle to the side of the center of the skull. Using a dental drill four small holes were made and bone cutters were used to cut a small cranial (4 mm diam.) opening over area 17. The dura remained undamaged. Additional holes were drilled further anterior to attach EEG screws. The animal was then placed on a small animal respirator and paralyzed with an initial intravenous dose of Gallamine Triethiodide (10 mg/kg).

During recording the animal was artificially respired with a mixture of 70% N₂O and 30% O₂. The stroke rate and volume were adjusted to maintain a peak end-tidal CO₂ concentration of about 3.8% or 33 mm mercury partial pressure as measured by infrared absorption. Paralysis was maintained with a constant infusion of Gallamine Triethiodide (10 mg/kg/h) and 5% dextrose in lactated Ringer's solution (10 ml/hr). Intravenous Pentobarbital Sodium (Nembutal) was administered continuously as an additional anesthetic (1 mg/kg/h). EEG recordings under these conditions are indicative of light anesthesia, and experiments (unpublished) in which the paralytic is withheld while the N₂O-Pentobarbital anesthetic is continued confirms that a state of light anesthesia and areflexia exists under these conditions. A feedback-controlled heating pad maintained the animal's temperature at 38° C. EEG, EKG, rectal temperature, blood pressure (measured through the tail), and end-tidal CO₂ were monitored throughout the experiment.

Following retinoscopic examination, appropriate contact lenses with 4-mm artificial pupils were selected to ensure that the eyes were in focus on a tangent screen 145 cm. distant. The locations of the optic disk and area centralis for each
eye were plotted on the tangent screen using a reversing ophthalmoscope.

Glass coated platinum-iridium electrodes with an impedance of approximately 500 kΩ (measured at 1 kHz) were used to penetrate the intact dura and isolate single neurons in Area 17. In Part III carbon fiber filled multibarrelled glass micropipets were inserted through a small hole placed in the dura (see methods Part III). The electrode was advanced using a motorized microdrive (Blasedale). Electrode penetrations were approximately either 0° or +5° from perpendicular to the anterior-posterior line. Penetrations continued to a depth of up to 6 mm along the medial bank of area 17 such that a number of ocular dominance and orientation columns were encountered during each penetration.

Signals from the electrode were amplified (x 1000), displayed on an oscilloscope, reproduced on an audio monitor, and fed into a window discriminator, which produced digital signals that could be registered by the computer. To ensure accurate isolation of single units, the waveform producing an output from the window discriminator was displayed on the oscilloscope and the shape and time course of the spike was monitored. In addition, the audio monitor could be driven by the window discriminator as well as the electrode output, thus allowing comparison with the visually observed raw spike signal.

Receptive fields of isolated units were initially located and categorized with moving and flashed stimuli using a hand held projector or computer generated bars, dots and gratings projected onto a tangent screen under manual control (see section on computer generated stimuli). The ocular dominance of the cell was then determined. Receptive field size and the orientation, length, and width of effective bar stimuli were also determined for stimulating through each eye. Qualitative assessments of the unit's direction and velocity selectivity were made using bars, and edges. The cell's responses to small spots of light were also tested. The stimulus projection system (either optic bench or Macintosh based projection system) was
then adjusted such that all subsequent stimuli were of the optimum orientation and length for each receptive field. Optic bench light stimuli had a luminance of approximately 80 cd/m² and contrast of between 70% and 80% while the Macintosh based system had a luminance which was slightly lower.

**Computer generated stimulus presentation**

Two separate computer systems were used to present stimuli, record responses, analyze data and produce figures. Much of the data from parts 1 and 2 were collected using a PDP 11/34, 11/23, 11/10 or 11/03. The hardware and software for these PDP systems were similar and could be used interchangeably for all parts of the experiments. An optic bench was used to project bars of light or square wave grating stimuli onto a tangent screen. The stimulus was illuminated by a 300-W tungsten projector bulb placed behind a condenser. An achromatic lens (with a focal length of 9 cm) front projected this image onto a tangent screen. To reach the screen the beam was first reflected approximately 90° using a small front-surface plane mirror mounted on a galvanometer (General Scanning type 300 PDT). This image then passed through a computer-controlled dove prism rotator, allowing the stimulus orientation to be changed, and was projected onto the tangent screen using a large front-surface plane mirror.

The optic bench stimuli were drifted across the receptive field under the control of a PDP-11/34 microcomputer using 12-bit digital to analog converters (DA's) driving a servo-controlled mirror galvanometer (time constant, 5 ms). A software package (POST) designed by Dr. Robert Douglas was used to control the stimuli and record the responses to 1 ms resolution. The Macintosh system could also drive the optic bench using the same DA's. Some of the data from parts 1 and 2 and all of the data from Part III were collected using a Macintosh FX computer and VAST
software (Douglas, 1990). Although similar to POST, VAST could be used to generate complex visual stimuli such as random dot patterns, Gabor patches, and dark and light bars and spots using a NUVISTA board. An Electrahoma large screen projector was used to display the stimuli on a front surfaced unidirectional tangent screen. A computer mouse could be used to manually move or flash stimuli on the tangent screen or the computer could carry out a complex series of stimulus presentations while collecting data, much of which could be analyzed on-line. Post-stimulus time histograms were generated and regardless of the computer system used to collect the data, much of the data were transferred into a Microsoft Excel spreadsheet for further analysis (see Analyzing Data).

Line-weighting functions

For each cell a line-weighting function was performed to test for the presence of ON and OFF subregions within the receptive field and to classify the cells as simple or complex on the basis of these subregions. The receptive field of each cell was divided into 15 subregions of equal size. An optimally oriented bar stimulus was flashed into a receptive field subregion for 200 ms during which time stimulus onset responses were collected (see Fig. 1). Stimulus offset responses were collected for 200 ms following the removal of the stimulus from the subregion. A line-weighting function of the cell's receptive field resulted from testing both ON and OFF responses at each of the fifteen receptive field subregions and spontaneous activity was assessed during an additional trial in which the stimulus remained well outside the receptive field. The order of presentation was randomized and each block of 16 stimulus presentations was repeated 32 times.

Analyzing Data

Data from across trials were often summed for a given cell and the number of action potentials occurring during the stimulus condition or a portion of the recording time was calculated. These raw data were transferred into a spreadsheet (Microsoft
Excel) and the responses for each stimulus condition were compared. Pre-adaptation spike records were compared to post-adaptation trials and in many cases the percentage change in responsivity was assessed for each stimulus condition. Regression equations were fit to scatterplots of the number of spikes during the pre-adaptation phase versus the post-adaptation phase for each stimulus condition. For more complicated equation fits, the data were transferred to the analysis program IGOR which allowed smoothing, linear interpolation, curve fitting to exponential, Gaussian, and Gabor equations, and graphing the data. Other Macintosh programs which were used to analyse data and construct tables and figures include: Statview 1 and 2, Cricket graph, Systat, Deltagraph, and Canvas. In addition, several IBM based programs were used to analyze some of the data in Part I. These include Lotus 123 and Grapl (a graphics and analysis program written by Dr. Nick Swindale in our lab).
Chapter 2

Position specific adaptation in simple and complex cell receptive fields of the cat striate cortex.

Simple cells typically have spatially distinct subregions which respond to either stimulus onset (ON regions) or stimulus offset (OFF regions). Ganz and Felder (1984) demonstrated that inhibitory interactions could occur over very small regions of the receptive field of a simple cell. They showed that ON and OFF regions could be further subdivided, based on the cell's responses to two bars presented sequentially (apparent motion) with very small spatial displacements (as little as 4 of arc), such that both stimuli were within a receptive field subregion. These and other similar studies (Swindale & Cynader, 1984) suggest that the receptive field ON and OFF subregions of a simple cell consist of smaller subunits which may interact to produce direction selectivity. Kulikowski, Rao and Vidyasagar (1981), using moving triangle waves, demonstrated that the ON and OFF subregions of simple cell receptive fields can adapt independently. Furthermore, they showed that adaptation within a receptive field subregion could alter the receptive field as a whole by altering the interactions between ON and OFF subregions. However, they did not indicate the nature of these interactions nor did they describe the extent to which the entire receptive field showed adaptation aftereffects.

In the present chapter the effects of prolonged stimulation of small areas within a cell’s receptive field subregion (either ON or OFF) were assessed. A bright bar of light was flashed at a rate of 2 Hz for a period of one minute at one receptive field position. The cell's responses to stimulation at many receptive field positions were then tested. By comparing the post-adaptation response profile to one obtained prior to adaptation it was possible to determine the effect of prolonged stimulation at the
point of adaptation. In addition, this allowed the assessment of the spread of the adaptation effect over the entire receptive field. The results of Kulikowski et. al. (1981) suggest that the ON and OFF regions of the simple cells might adapt independently. Furthermore, there may be some adaptation-induced interactions which may reflect adaptation of inhibitory connections between the two antagonistic subregions. If Ganz and Felder (1984) are correct, and ON and OFF subregions can be subdivided, then it should be possible to adapt small portions of these receptive field subregions thereby revealing the size of the underlying subunits.

Simple cells and complex cells have been shown to have different types and amounts of facilitatory and inhibitory interactions within the receptive field (Baker, 1988; Bishop et al., 1974; Emerson et al., 1987; Hamilton, Albrecht, & Geisler, 1989; Hawken & Parker, 1987; Heggenlund, 1984; Jones & Palmer, 1987; Jones, Stepnoski, & Palmer, 1987; Kato, Bishop, & Orban, 1978; Kulikowski, Marcelja, & Bishop, 1982; McLean & Palmer, 1989; Movshon et al., 1978a; Movshon et al., 1978b; Peterhans, Bishop, & Camarda, 1985; Szulborski & Palmer, 1990; Yamane, Maske, & Bishop, 1985). Complex cells also differ from simple cells in the spatial relationship between ON and OFF regions (Albus, 1980; Bishop et al., 1974; Bishop, Kato, & Orban, 1980; DeValois, Yund, & Hepler, 1982; Ganz, 1984; Gaska, Jacobson, & Pollen, 1988; Goodwin et al., 1975; Hawken & Parker, 1987; Hubel & Wiesel, 1962; Jones et al., 1987; Kulikowski et al., 1982; Kulikowski & Vidyasagar, 1986; McLean & Palmer, 1989; Movshon et al., 1978a; Movshon et al., 1978b; Orban, Kennedy, & Bullier, 1986; Orban, Kennedy, & Maes, 1981; Peterhans et al., 1985; Sillito, 1977; Sillito, Kemp, Milson, & Berardi, 1980; Tanaka, 1983; Yamane et al., 1985; Zumbroich, Price, & Blakemore, 1988). In simple cells, ON and OFF subregions are largely non-overlapping while in complex cells the ON and OFF regions overlap. Most relevant to this thesis are the reports on the adaptation of simple and complex cells. Early electrophysiological adaptation research suggested that simple cells showed adaptation aftereffects but complex cells did not (Maffei et al., 1973). Maffei
(1973) suggested that either complex cells did not adapt or they recovered almost immediately. More recently, however, complex cells have been shown to adapt as well as simple cells (Albrecht et al., 1984; Dean, 1983; Hammond & Mouat, 1988; Hammond et al., 1989; Marlin et al., 1988; Ohzawa et al., 1985; Sclar et al., 1989). Although complex cells showed adaptation time courses and asymptotic declines in responsivity equal to those for simple cells there was a significant difference in the direction selective adaptation between simple and complex cells (Marlin et al., 1988). Specifically, simple cells showed much greater changes in direction selectivity following prolonged unidirectional stimulation. Complex cells showed more nonspecific effects with both preferred and nonpreferred direction responses decreasing equally (Marlin et al., 1988). Following nonpreferred direction adaptation the direction selectivity scores for simple cells increased but did not change significantly for complex cells (Marlin et al., 1988).

Complex cells have overlapping receptive field subregions and the direction selectivity is the result of nonlinear interactions, and therefore it is possible that the position specific adaptation in complex cells in similar experiments would be different to that observed in simple cells under the same adapting conditions. In complex cells the ON and OFF subregions overlap and therefore one would expect the ON and OFF channels to adapt similarly to prolonged single receptive field position stimulation.

The specific question which these experiments address is: Will the adaptation effects be localized to the region of the receptive field subjected to the prolonged stimulation or will the cells responses be reduced throughout the receptive field? If the adaptation at a single point in the receptive field results in a general reduction of activity in the cells then this would suggest that the adaptation is the result of a general process which affects the firing rate of the cell. Adaptation effects localized to the region subjected to prolonged stimulation would suggest a more local
mechanism of adaptation on specific synapses or dendrites which are most stimulated during the adaptation period.

**Methods**

The position specific adaptation of 25 visual cortical simple cells and 22 complex cells was investigated in 15 cats. The methods for recording single unit activity from the striate cortex of acutely prepared anesthetized cats have been described in detail in the general methods.

*Experimental procedure*

Figures 1 and 2 describe the procedure used during the adaptation experiments for both simple and complex cells, respectively. An optimally oriented bar stimulus was flashed at a receptive field position (RFP) for 200 ms during which time stimulus onset responses were collected (see Fig. 1 A). Stimulus offset responses were collected for 200 ms following the removal of the stimulus from the RFP. A 50 ms interval separated the offset of the stimulus and the collection of OFF responses to allow for the cessation of ON responses. This did not eliminate the collection of any OFF responses as cells in area 17 have a response latency typically greater than 50 ms. A line-weighting function of the cell's receptive field was obtained from both ON and OFF responses at each of 15 RFPs (spaced .10, .25, .50 or 1° apart). Spontaneous activity was assessed in an additional trial in which the stimulus remained well outside the receptive field (see Fig. 1 B). The order of presentation was randomized and each block of 16 stimulus presentations was repeated 32 times. The bar of light was then flashed ON and OFF for 60 s at a rate of 2 Hz at one of the 15 RFPs. Immediately following this adaptation run the stimulus was flashed ON and OFF at each of the 16 RFPs to assess the effects of the adapting stimulus. This adaptation and post-adaptation test sequence was repeated 32 times with the adapting
The procedure for deriving line weighting functions and the spatial wavelength ($\lambda$) of simple cells in Area 17 of the cat striate cortex. An optimally oriented slit of light (0.1 - 0.5 degrees of visual angle) was flashed onto each of 15 RFPs for a period of 200 ms. Each 500 ms recording time (Rec time) consisted of an initial wait period of 50 ms, a 200 ms period during which time stimulus onset responses were collected, a 50 ms wait period following cessation of the stimulus and a 200 ms period during which stimulus offset responses were collected. The responses were analyzed in 50 bins of 10 ms each and an example of this analysis for 16 repetitions (sweeps) is shown for receptive field positions 6 through 13 in panel A. In panel B the stimulus onset responses were summed for each receptive field position and are plotted as positive histogram bins, while OFF responses are plotted as negative (filled) histogram bins. The differences in the ON and OFF histograms for each receptive field position were calculated and used as an indication of the spatial segregation of the ON and OFF receptive field subregions within a simple cell. A best Gabor function fit to this difference plot was used to obtain a quantitative measure of the wavelength ($\lambda$) of the simple cell (see panel C).
Responses

Stimulus

Pre-test (t = 256s)
32 repetitions of each stimulus position condition (randomly presented)

Adaptation And Post-test Cycle (t = 2,432s)
120 repetitions of one stimulus position condition (randomly presented)

1 repetition of each stimulus position condition
(t = 60s)
(t = 8s)

Repeat 32 times
The procedure for deriving line weighting functions of complex cells in Area 17 of the cat striate cortex and the adaptation paradigm used for adapting small regions of the receptive field. An optimally oriented slit of light (0.1 - 0.5 degrees of visual angle) was flashed onto each of 15 RFPs for a period of 200 ms. Each 500 ms recording time (Rec time) consisted of an initial wait period of 50 ms, a 200 ms period during which time stimulus onset responses were collected, a 50 ms wait period following cessation of the stimulus and a 200 ms period during which stimulus offset responses were collected. The responses were analyzed in 50 bins of 10 ms each and an example of this analysis for 16 repetitions (sweeps) is shown for receptive field positions 6 through 13 in panel A. In panel B the stimulus onset responses were summed for each receptive field position and are plotted as positive histogram bins, while OFF responses are plotted as negative (filled) histogram bins. The sum of the ON and OFF histograms for each receptive field position were calculated and the standard deviation of a best Gaussian function fit to this sum plot was used as a quantitative measure of the size of the receptive field (see panel C). Panel D shows the sequence and duration of conditions in the adaptation experiments for both simple and complex cells.

Figure 2 caption

The procedure for deriving line weighting functions of complex cells in Area 17 of the cat striate cortex and the adaptation paradigm used for adapting small regions of the receptive field. An optimally oriented slit of light (0.1 - 0.5 degrees of visual angle) was flashed onto each of 15 RFPs for a period of 200 ms. Each 500 ms recording time (Rec time) consisted of an initial wait period of 50 ms, a 200 ms period during which time stimulus onset responses were collected, a 50 ms wait period following cessation of the stimulus and a 200 ms period during which stimulus offset responses were collected. The responses were analyzed in 50 bins of 10 ms each and an example of this analysis for 16 repetitions (sweeps) is shown for receptive field positions 6 through 13 in panel A. In panel B the stimulus onset responses were summed for each receptive field position and are plotted as positive histogram bins, while OFF responses are plotted as negative (filled) histogram bins. The sum of the ON and OFF histograms for each receptive field position were calculated and the standard deviation of a best Gaussian function fit to this sum plot was used as a quantitative measure of the size of the receptive field (see panel C). Panel D shows the sequence and duration of conditions in the adaptation experiments for both simple and complex cells.
Figure 2
stimulus always presented to the same RFP and the order of stimulus presentation in the post-adaptation test always randomized. The 32 repetitions of the adaptation and post-test cycle took 36 minutes to complete while the pre-adaptation test took 4 minutes. For each cycle the post-adaptation testing was completed within 8 s, before the cell recovered from the previous 60 s adaptation period. The 8 s test period was divided into 16 different 500 ms blocks such that 1 position was tested in each block. This arrangement of post-adaptation stimulus presentations ensured that over the course of the 32 sweeps each RFP was tested an average of 2 times in each of the 500 ms blocks (see Fig. 2 D). This ruled out any positional biases resulting from decay of the adaptation effects during the 8 s test period.

The receptive fields of simple cells can be well approximated by a Gabor function with the wavelength ($\lambda$) equal to approximately twice the distance from the peak of the ON region to the trough of the OFF region. The wavelength value is derived by obtaining the parameters of the least squares Gabor function which best fits the spatial positions of the ON and OFF subregions of a simple cell's receptive field (Baker & Cynader, 1986). The wavelength of this Gabor function has been related to the spatial frequency tuning of a particular neuron and is approximately the reciprocal of the neuron's preferred spatial frequency (Baker & Cynader, 1986; Kulikowski et al., 1981; Movshon et al., 1978a; Movshon et al., 1978b). Equation (1) is the equation of the Gabor function equation that was used to fit our data, and Figure 1 C shows an example of the type of fit that is obtained.

$$Y(x) = A e^{-\frac{(x-x_0)^2}{2s^2}} \cos(\frac{2\pi x}{\lambda} + \phi) \quad (1)$$

The fitted parameters were the maximum amplitude of the response ($A$), the receptive field center ($x_0$), width ($s$), wavelength ($\lambda$), and phase ($\phi$).
The receptive fields of complex cells are characterized by overlapped ON and OFF regions and can be best described using a Gaussian equation (see Figure 2).

Histograms for ON and OFF responses were derived for each of the 16 stimulus positions by summing spikes occurring in a 200 ms recording epoch (see Fig 1). For each cell the spontaneous activity was subtracted and the data were then summed across the 32 stimulus repetitions. Each cell was carefully tested to ensure that the receptive field location did not shift due to uncontrolled eye movements during the adaptation experiments. These tests included a number of pretests spaced between 5 and 20 minutes apart as well as tests for recovery from adaptation at intervals of 5 and 10 min following cessation of the adaptation run. Only cells with high signal-to-noise ratios and good receptive field stability were used. Twenty five simple and 22 complex cells were judged to be sufficiently stable during the adaptation experiments to warrant further analysis.

Results

The adaptation procedure used in the present experiment did not produce response decrements as large as in experiments involving whole field adaptation with moving stimuli (Albrecht et al., 1984; Dean, 1983). The major differences lie in the magnitude and reliability of the cell's response to the adapting and test stimuli. Static flashed stimuli were not as effective in evoking neuronal responses as moving stimuli and the amount of observable adaptation was much less. Nevertheless, in some cells we were able to reduce responses by as much as 84%. 
The pre- and post-adaptation line weighting functions of a typical simple cell (cell # sp26) are shown in panels A and B, respectively. The size of the receptive field and the light stimulus (bar) used during stimulation are shown in degrees of visual angle at the upper left of panel A. In addition, the position of the bar indicates the relative position of the light stimulus during prolonged stimulation. Stimulus onset responses for each receptive field position are displayed as positive histogram bins (unfilled bars) while stimulus offset responses are negative histogram bins (filled bars). In the line-weighting function graphs (panels A and B) negative histogram bars do not indicate decreased responding. Rather they indicate an increase in responsivity when the stimulus is removed from the receptive field position. In each panel the spontaneous activity has been subtracted from the line-weighting profile. The abscissa shows the distance from the point of adaptation in degrees of visual angle. The arrow indicates the position of the stimulus during adaptation trials. Panel C and D show the adaptation-induced changes in the ON and OFF responses (respectively) of the cell at each receptive field position. Panel E shows the Gaussian fit to the pre-adaptation ON response profile. The standard deviation (s) of the Gaussian was used as a measure of the size of the receptive field ON subregion. Panel F shows the Gaussian fit to the response decrement profile for ON responses (from panel C). This profile was used to obtain a measure of the spread of adaptation across the receptive field subregion.
Adaptation to position in simple cells

The simple cell (sp26) was repeatedly stimulated in the center of its ON region (at the position labelled 0 in Fig. 3 A) and shows the typical adaptation effects from prolonged local stimulation. This cell showed a very localized region of adaptation-induced decrements of ON responses. Prior to adaptation, this cell's response to stimulation at the point of adaptation was 123 spikes in the 32 sweeps. Following adaptation, the responses declined by 17.8% to 101 spikes. Responses in the receptive field position adjacent to the point of adaptation dropped by 52% from 110 to 58 spikes. No other receptive field position displayed such a dramatic decrease in responsivity. Strikingly, other positions contained within the ON region and adjacent to these two points displayed increased responsivity following adaptation (Fig. 3 C). Prolonged stimulation in the ON responding region had minimal effects on the neighboring OFF region (Fig. 3 D). The receptive field subregions could be well approximated by a Gaussian equation (see equation 2) and panel E shows the Gaussian equation fit to the profile of ON responses for the example cell sp26. The standard deviation (s) of the Gaussian was taken as a measure of the size of the receptive field subregion. In addition we also fit a Gaussian equation to the adaptation-induced response decrement profile (Fig. 3 C) and used the standard deviation of this Gaussian as a measure of the spread of the adaptation across the receptive field (panel F).

\[ Y(x) = k + Ae^{-(x-x_0)^2/2s^2} \]  \hspace{1cm} (2)

ON region adaptation in the cell shown in Figure 4 A resulted in response decrements around the site of adaptation to some degree in the neighboring OFF region (not shown). This cell showed a typical facilitation of ON responses at receptive field positions which were not subjected to prolonged stimulation. This
cell experienced prolonged stimulation near the center of its ON region and displayed an 84% decrease in responsivity at the point of adaptation (from 128 to 21 spikes in 32 sweeps). The two positions adjacent to the point of adaptation displayed small reductions to stimulus onset following adaptation while the RFPs further to the left of the point of adaptation displayed increased responsivity. The odd-symmetric cell whose responses are shown in Fig. 4 B was also subjected to prolonged stimulation in the center of the ON region but showed adaptation in each RFP in the ON region adapted. Following adaptation, the point of adaptation showed a 38% reduction in responsivity. The adaptation effect was visible throughout the ON region and the points adjacent to the point of adaptation also showed large reductions in firing. There were no changes in stimulus offset responsivity at any point in the receptive field even though there was some spatial overlap with the ON region. Fig. 4 C shows the responses from an even symmetric simple cell which was exposed to prolonged stimulation in the center of its OFF region. The pattern in this cell was atypical in that both the ON and the OFF responses showed a similar pattern of adaptation effects even though only the OFF region was stimulated. The OFF response prior to adaptation was characterized by a central area of OFF excitation, flanked on either side by inhibitory regions in which the stimulus offset responses were below the level of spontaneous activity (Fig. 4 C, left panel, filled bars). These inhibitory side regions were located at the same RFPs as the two ON regions (unfilled bars). The stimulus onset response in the center of the OFF region was also below the level of spontaneous activity. Following prolonged stimulation in the center of the OFF region, the responsivity to stimulus offset at that point was reduced by 19% (Fig. 4 C, right panel). RFPs close to this region showed responsivity reductions to both the stimulus onset and stimulus offset. However, in the flanking side regions the adaptation procedure increased the response to stimulus offset such that the responses
Figure 4 caption

The left side of each panel shows the pre-adaptation line-weighting profiles for three typical simple cells tested for position specific adaptation. The size of each receptive field and light stimulus (bar) used during stimulation for each cell are shown in degrees of visual angle at the upper left of each of the pre-adaptation line-weighting function panels. In addition, the position of the bar indicates the relative light stimulus position during prolonged stimulation (marked with an arrow in panels A-C). Stimulus onset responses for each receptive field position (RFP) are displayed as positive histogram bins (unfilled bars) while stimulus offset responses displayed as negative histogram bins (filled bars). In the pre-adaptation line-weighting functions, negative histogram bars do not indicate decreased responding. Rather they indicate an increase in responsivity when the stimulus is removed from the receptive field position. In each case the spontaneous activity has been subtracted from the line-weighting profile. The abscissa shows the distance from the point of adaptation in degrees of visual angle.

The right side of each panel shows the adaptation-induced change in the number of spikes for each receptive field position for the subregion adapted (only stimulus onset responses are shown for panels A & B and stimulus offset responses for panel C). The effect of prolonged stimulation on the antagonistic subregions (those not stimulated during adaptation) was less marked and is discussed in the text. Negative histogram bins reflect an adaptation-induced decrease in the number of spikes at that receptive field position while positive bins reflect an increase in firing. In each case the adaptation was strongest around the point of adaptation and the adaptation effects decreased as the distance from that point increased.
at these positions became excitatory rather than inhibitory. Although there was no initial stimulus onset response at the point of adaptation, the adapting stimulus had a profound effect on the two ON lobes (not shown). RFPs close to the point of adaptation decreased their responsivity to stimulus onset (to a level below spontaneous activity) whereas positions further away increased responsivity.

Although the adapting stimulus was usually presented at or near the peak of the RF subregion, in many cells additional tests were made in another RF subregion or at a number of different RFPs within the same subregion. Tests were also made with whole field adapting stimuli but the cells typically did not respond well to whole field stimuli and so the adaptation effects were not strong. Furthermore, experiments done with moving gratings as the adapting stimuli produced adaptation effects which were uniform across the receptive field.

Adaptation at different RFPs showed that the peak of the response decrement was always centered around the point of adaptation regardless of its spatial location within the receptive field. Cell su10-03 is shown as an example of the effects of adaptation at three different RFPs within the same cell's OFF region. The different experiments were separated by at least 30 minutes and a number of post adaptation recovery tests were performed to ensure that receptive field profile had recovered from the previous adaptation trials. Although the magnitudes of the response decrements were different for each adaptation position, the results clearly show that the adaptation-induced response decrements were strongest at the point of adaptation. Furthermore, each panel shows that the adaptation did not induce a general decline in responsivity as there were RFPs which maintained a high response rate and appeared to be completely unaffected by the adaptation stimulus only 1° away. Note that in all three panels of Fig. 5 there is an asymmetric spread of adaptation, regardless of the adapting position, such that RFPs located to the right of the adapting stimulus were
The OFF response profiles before and after adaptation for an odd symmetric simple cell are shown in the left of panels a-c. In each of the left panels the pre-adaptation data are represented by asterisks while the post-adaptation data points are filled circles. The abscissa represents the fifteen receptive field positions which were stimulated randomly both prior to and following adaptation at one RFP. The arrows in each panel show the RFP which underwent prolonged stimulation. The right side of each panel shows the change in responsivity at each RFP following adaptation. The peak of the adaptation-induced response decrement is located at the point of adaptation in each of the three panels and not at the peak of the pre-adaptation OFF response profile.
affected more than RFPs equally distant but to the left. This asymmetry is further illustrated in Figure 8 and is considered in the discussion for this chapter.

*The spatial spread of adaptation in simple cells*

We quantified the spread of adaptation across the receptive field using the standard deviation ($s_2$) of the best Gaussian curve fit to the response decrement profile for each cell (see Figure 3 F). The results of this analysis revealed that the spread of adaptation fell along a continuum with values of $s_2 < 0.5^\circ$ for most cells. We quantified the size of the receptive field subregion using the standard deviation ($s_1$) of the best Gaussian curve fit to the pre-adaptation response profile (see Figure 3E). We then compared the size of the receptive field subregion ($s_1$) with the spread of adaptation ($s_2$) by taking a ratio ($R_s = s_1/s_2$) for each cell. Thus adaptation spreading throughout an entire RF subregion would be represented by $R_s = 1$, while adaptation spreading through only 1/2 would yield $R_s = 2$. Three subgroups are immediately apparent in the frequency distribution of these ratios (Fig. 6 A). The first group of cells (black bars) has a mean ratio of $\bar{R}_s = 1.06$ indicating that the adaptation encompasses the entire RF subunit. The second group (grey bars) had a larger mean ratio ($\bar{R}_s = 2.08$) indicating that the adaptation spreads through only 1/2 of the RF subunit. The final group has only two cells which have very large ratios ($\bar{R}_s = 4.36$) and show very localized adaptation.

We compared the wavelength of the receptive field to the spread of adaptation ($R_\lambda = \lambda_1/s_2$) through the receptive field subregion by taking the ratio of the wavelength of the best fit Gabor function (see Fig. 1) to the standard deviation of the respective best fit Gaussian for the response decrement data (see Figure 6 D). One cell had a $R_\lambda > 40$ and was not included in panel D but was included in the scatterplots in panels C and F. Unlike the ratio of the size of the receptive field ON
Panel A shows a frequency distribution of the ratio of the size of the receptive field subunit prior to adaptation to the size of the adaptation effect for all cells. The size of the receptive field subregion was defined as the standard deviation ($s_1$) of the best Gaussian curve fit to the partial receptive field profile (either ON or OFF responses). The size of the adaptation effect was defined as the standard deviation ($s_2$) of the best Gaussian fit to the adaptation-induced changes in responsivity for the subregion adapted. A ratio of $R_s = s_1/s_2 = 1$ indicates that the adaptation effects spread throughout the receptive field subregion. An $R_s = 2$ indicates that the adaptation effects spread through only 1/2 the subregion. Panel A shows that the population of simple cells falls into three significantly distinct groups based on the values of $R_s$. Adaptation at one receptive field position can spread throughout the subregion, or through 1/2 or 1/4 of the subregion. Panel B shows a scatterplot of the size of the receptive field plotted against the spread of adaptation across the receptive field for each group described above. Panel C shows a scatterplot of the wavelength of the receptive field subregions plotted against the spread of adaptation for the three groups described in panel A. The spread of adaptation is not significantly related to the spatial wavelength of the receptive field and therefore the regression equations for these data are not shown. Panel D shows a frequency distribution of the ratio of the wavelength of the receptive field prior to adaptation to the size of the adaptation effect ($R_\lambda = \lambda/s_2$) for all cells. The cells fall loosely into two groups, but these two groups are not as distinct as with the groupings based on the $R_s$ ratios described in panel A. Panel E shows the spread of adaptation plotted against the size ($s_1$) of the subregion adapted for the two groups described in panel D. Notice that although the data are the same as those shown in panel B, the cell groupings define a different relationship between the size of the receptive field and the spread of adaptation (see text). Panel F shows the spread of adaptation plotted against the spatial wavelength of the receptive field for the two groups described in panel D.
or OFF zone to the spread of adaptation (see Fig. 6 A), the cells did not fall into three distinct groups but instead showed a tendency to fall into two groups. Although the initial firing rates and the magnitudes of the response decrements were different for each cell there was no difference between the different subpopulations described in panels A or D based on these measures.

To enable us to average the adaptation effects at each point in the receptive field it was necessary to normalize the spatial scale of each receptive field. Because it was possible to subdivide the cells into subpopulations on the basis of \( R_s \) or \( R_{\lambda} \), we wanted to determine which of these produced more heterogeneous subgroups. The correlation between the size of the receptive field subunit stimulated and the spread of adaptation across the receptive field \( (r^2 = .395) \) became much stronger when this correlation was calculated separately for each of the three subgroups described in panel A (see Fig. 6 B). Regression equations fit to the first two series of data reveal slopes of 0.928 and 1.869, respectively, and correlation coefficients of 0.909 \( (F=100.02, P<.0001) \) and 0.951 \( (F=175.25, P<.0001) \), respectively. Using \( R_{\lambda} \) to classify cells into groups was clearly not as effective as using \( R_s \) because there was no decrease in the variability associated with each regression equation and there was no improvement over the correlation statistic taken for the entire population of cells (see Figure 6 D). Cells with \( R_{\lambda}>15 \) had a smaller spread of adaptation scores and the subunit size also tended to be smaller in these cells. Regression equations fit to the low and high \( R_{\lambda} \) groups reveal slopes of .404 and .344, respectively, and correlation coefficients of 0.407 \( (F=8.92, P<.02) \) and 0.344 \( (F=4.202, P>.05) \). If the spread of adaptation is plotted against the wavelength of the receptive field then the correlation coefficient for all the cells was very low \( (r^2 = .069) \) and using \( R_{\lambda} \) to classify the cells produced only marginal gains in the correlations (Figures 6 C and F). The correlation coefficients for the regression equations fit to the groups of cells
with \( R_s = 1 \) and \( R_s = 2 \) were \( r^2 = 0.027 \) and \( r^2 = 0.197 \), respectively, and were not included in Fig. 6 C. Using the cell classification described in Fig. 6 D the regression equations fit to the low and high \( R_s \) groups reveal slopes of 16.099, and 3.60, respectively, and correlation coefficients of 0.376 (\( F = 7.846, P < .02 \)) and 0.753 (\( F = 24.356, P > .001 \)) respectively (Figure 6 F).

These analyses thus reveal that the spread of adaptation relates well to the size of the receptive field subunit and rather less well to the spatial wavelength of the cell. Furthermore, the different degrees of spread of adaptation in the groups described in Figure 6 had to be considered when averaging the adaptation effects for the population of cells.

Cells in which the prolonged stimulation was confined within an ON region of the receptive field displayed adaptation effects which were similar to those observed in cells in which the prolonged stimulation was within an OFF subregion. There was no significant difference between ON versus OFF region adaptation at any point in the receptive field. Therefore, we combined the results of adaptation within ON regions with those of OFF regions in subsequent analyses. The RFPs of each cell were converted to distance from the point of adaptation either in \( \lambda \) or in \( s \) (see Fig. 6). We decided to continue to use both measures of receptive field size for the following reasons. Although the wavelength of the cell proved inadequate for subdividing the population and was only weakly correlated with the spread of adaptation, the wavelength of a simple cell has been shown to be highly correlated with the optimal distance for apparent motion and therefore is thought to be important for direction selectivity. The relationship between wavelength and the spread of adaptation became more interesting when the direction selectivity was also considered (see Figure 8). We continued using \( s_1 \) as a measure of the receptive field size as it allowed us to average the population as a whole and to compare this to the...
averaged data from each of the three subpopulations described in Figure 6 A.

The Gaussian or Gabor fit process made the population of cells impossible to average directly because the location of the RFPs in s or λ units was unique to each cell. To allow us to average the adaptation effects at comparable distances from the point of adaptation in each cell, the adaptation profile for each cell was subjected to a linear interpolation process yielding 100 points from the original 15 RFPs. The mean percent change in response at the point of adaptation and at 0.2λ or 0.25 s intervals could then be averaged. The mean adaptation-induced response decrements for the entire population of cells subjected to this analysis are shown in Figure 7. The left panel shows the mean change in responses with receptive field wavelength as the unit of distance from the point of adaptation whereas the right panel illustrates the spatial spread of these effects when the size of the subregion is used as the unit of distance. The adaptation was strongest at the point of adaptation and the adaptation effects decreased as the distance from this point increased. Within 0.1 λ or 0.25 s from the point of adaptation the mean adaptation-induced response decrement was significantly different from zero. Similar effects were observed in each of the subgroups described in Figure 6 with different degrees of spread of adaptation in each group.

**Asymmetric spread of adaptation across the receptive field of simple cells**

The data presented in Figure 7 have been analyzed such that points equidistant from the point of adaptation were summed regardless of the cell’s direction selectivity. This produced adaptation-induced response decrement profiles which closely resemble a Gaussian function. The results of this analysis suggest that there is a general decline in responsivity, where the magnitude of the decrement is dependant strictly on the proximity to the adaptation site. Yet, it was our impression that the adaptation effects were more specific than those indicated by Figure 7 and
The mean adaptation-induced percent change in response is plotted against the distance from the point of adaptation using either wavelengths (panel A) or receptive field size (panel B). The RFPs of each cell were converted to distance from the point of adaptation in both standard deviations (see Fig. 3) and wavelengths (see Fig. 1) and the adaptation profile for each cell was subjected to a linear interpolation so that means could be taken at fixed distances (in either λ or s) from the point of adaptation. A mean percent change in response was obtained for the point of adaptation and for 0.2λ and 0.25s points distant. RFPs equidistant were pooled and displayed symmetrically around the point of adaptation. An asterisk indicates a receptive field position for which the adaptation-induced change in responsivity was significantly different from zero (at p < .05).
**A**

- **Mean Change In Number Of Spikes**
- **Distance from Point of Adaptation ($\lambda$)**

**B**

- **Mean Change In Number Of Spikes**
- **Distance from Point of Adaptation ($s_1$)**

*All cells*
Figure 8 shows the spread of the adaptation when the receptive fields for the cells have been aligned with respect to their preferred directions of motion. A bar of light moving across the receptive field in the cells preferred direction would pass RFP 0 λ or 0 s before passing positions to the right. A bar of light moving in the nonpreferred direction would pass RFP 0 λ or 0 s before passing through positions to the left of 0. Each cell grouping described in Figure 6 produced a similar asymmetric spread of adaptation effect which was related to the cell's direction selectivity. The adaptation spread asymmetrically with larger declines in responsivity at preferred side RFPs than for equidistant points located on the nonpreferred side of the point of adaptation.
that asymmetries in individual profiles (see for example Fig 4 A and B) were not uncommon. Figure 8 shows the results of analyzing the data of Figure 7 such that the line-weighting function for each cell was aligned based on the cell's direction selectivity. To do this the orientation of each cell's receptive field was rotated such that the preferred direction of stimulus motion of each cell was aligned with all other cells in the population. The mean percent change in response at the point of adaptation and at 0.2 λ and 0.25 s points distant were then averaged. RFPs with positive distances from the point of adaptation (to the right of zero) would be stimulated by a bar of light originating at the point of adaptation and moving in each cell's preferred direction. RFPs with negative distances from the point of adaptation (to the left of zero) would be stimulated by a bar of light beginning at the point of adaptation and moving in the cell's nonpreferred direction. Figures 8 A and B show the spread of adaptation of all cells as a function of positions corresponding to the units preferred and nonpreferred direction of motion.

It is clear that there is an asymmetrical spread of adaptation across the receptive field which is correlated with the direction selectivity of the cells. Adaptation effects were strongest at the point of adaptation and at RFPs on the preferred direction side of this point. Response decrements were significantly different from zero at the point of adaptation and at points up to 0.2 λ (Fig. 8 A) and 1.5 s distant (Fig. 8 B). Although spread of adaptation across the receptive field was different for each group of cells described in Figure 6, the directional asymmetry in the spread of adaptation was present in each group of cells. Furthermore, the areas of the receptive field which displayed increased responsivity were always located on the nonpreferred side of the receptive field and were closer to the point of adaptation in the large ratio groups than in the small ratio groups. Although the spread of adaptation was different between these groups of cells, within each group the regions of facilitation
Mean response decrement scores for RFPs in the preferred direction were subtracted from scores in the nonpreferred direction for points equidistant from the point of adaptation (error bars indicate standard error). Difference scores less than zero represent larger response decrements for RFPs in the preferred direction than in the nonpreferred direction. An asterisk indicates a receptive field position at which the directional asymmetry (P spread - NP spread) was significantly different from zero (at p < .05). Strong asymmetrical spread of adaptation was observed in each of the groups of cells outlined in Fig. 5 and were pooled in this figure. The adaptation spread asymmetrically across the receptive fields of the simple cells and the directional asymmetry of the spread of adaptation was greatest at 0.2 λ and 1.0 s from the point of adaptation.
and adaptation occurred at approximately the same receptive field positions.

To further quantify this directional asymmetry, scores in the preferred direction for each individual cell were subtracted from scores in the nonpreferred direction for points equidistant from the point of adaptation. Mean directional asymmetry scores less than zero represent points in the adaptation profile at which there was more adaptation at points corresponding to preferred direction stimulation than nonpreferred direction stimulation. Paired t-tests show the mean \((n=25)\) directional asymmetry to be significant from \(0.2\ \lambda\) to \(0.6\ \lambda\) and from \(0.5\ \text{s}\) to \(1.0\ \text{s}\) from the point of adaptation (see Figure 9 A and B). In each group of cells described in Figure 6, the directional asymmetry was greatest at \(0.2\ \lambda\) and \(1.0\ \text{s}\) and decreased as the distance from the point of adaptation increased.

**Binocular effects in simple cells**

The ON responses of a binocular simple cell which responded strongly to stimulus onset and had very weak OFF responses were strikingly similar when the cell was stimulated through the non-dominant eye ("unstimulated eye"), even though the firing rate evoked was much lower (see Fig. 10). The adapting stimulus was presented monocularly in the center of the ON subregion. When the receptive field was stimulated through the "test eye", there was a 44% decrease in responsivity at the point of adaptation (Fig. 10 C). The adaptation effect was also very strong at adjacent points in the "test eye" receptive field. When the stimulus was presented to the "unstimulated" eye the receptive field showed a similar adaptation effect even though it did not directly experience the prolonged stimulation during the adaptation phase (Fig. 10 D). Figures 10 E-H show another example of intraocular transfer of position specific adaptation in a binocular even-symmetric simple cell adapted in the center of its ON region (OFF responses not shown). For both the "test" and
Figure 10 caption

Results of interocular transfer tests of position specific adaptation are shown for two binocularly driven simple cells. The size of each receptive field and bar used during stimulation for each cell are shown in degrees of visual angle at the upper left of panels A and E. In addition the position of the bar indicates the relative bar position during prolonged stimulation. For Panels A, B, E and F, the pre-adaptation stimulus onset responses for each receptive field position are displayed as positive histogram bins (unfilled bars). In each case the spontaneous activity has been subtracted from the line-weighting profile. The abscissa shows the distance from the point of adaptation in degrees of visual angle. In panels C, D, G, and H, negative histogram bins reflect an adaptation-induced decrease in the number of spikes at that receptive field position while positive bins reflect an increase in post-adaptation firing. Panels A and E show the pre-adaptation stimulus onset responses for stimuli presented monocularly though the same eye as the adapting stimulus (test eye). Panels B and F show the onset responses for stimuli presented though the opposite eye to the adapting stimulus (unstimulated eye). The adaptation effects were strongest near the point of adaptation in the adapted (panels C and G) and in the unstimulated eye (panels D and H) showing clear interocular transfer of the adaptation.
A Test Eye

B Unstimulated Eye

Number of Spikes

Change in Number of Spikes

Distance from Point of Adaptation (in wavelengths)

Distance from Point of Adaptation (in wavelengths)
"unstimulated" eyes the adaptation spread throughout the ON region (Figs. 10 G and H) and into neighboring OFF regions. Three of the four binocular cells tested for intraocular transfer showed strong position specific adaptation and strong intraocular transfer. The fourth cell showed very weak adaptation which did not transfer to the "unstimulated" eye.

Adaptation to position in complex cells

Complex cells exhibited adaptation effects which were similar to those shown by the simple cells. Prolonged stimulation at a single receptive field position resulted in a change in the receptive field profile as assessed with both ON and OFF responses. In many cases the adaptation effects were limited to either the On or OFF responses despite the light slit adapting stimulus evoking both ON and OFF responses.

The complex cell shown in Figure 11 showed adaptation effects typical of the population. The adaptation effects were greatest at the point of adaptation and decreased with distance from this point. Both the ON and the OFF responses showed these adaptation effects. The greatest the response decrement for the ON profile was located right at the point of adaptation. The OFF response decrement profile (panel D) was offset from the point of adaptation but still displayed a large reduction in responses. Both the ON and the OFF response profiles showed adaptation effects which were asymmetric and which were related to the direction selectivity of the cell (see panels B and D). Receptive field positions on the preferred direction side of the point of adaptation displayed greater adaptation aftereffects than did receptive field positions equidistant from the adaptation site, but on the nonpreferred direction side of the receptive field.
The pre- and post-adaptation receptive field profiles for the ON and OFF responses of a typical complex cell (c3.1) are shown in panels A and C (respectively). Solid black lines represent the total number (in 32 repetitions) of pre-adaptation responses at each of the 15 points in the receptive field while the shaded grey lines show the post-adaptation responses at these same receptive field positions. The difference between the pre- and post-adaptation values are shown in Panels B and D. The arrow in each panel shows the position in the receptive field which was stimulated at 2 Hz during the 60 seconds of adaptation on each trial. In this cell the adaptation-induced response decrements were apparent in both the ON and OFF profiles.
The pre- and post-adaptation receptive field profiles for the ON and OFF responses of a typical complex cell (su306) are shown in panels A and C (respectively). Solid black lines represent the total number (in 32 repetitions) of pre-adaptation responses at each of the 15 points in the receptive field while the shaded grey lines show the post-adaptation responses at these same receptive field positions. The difference between the pre- and post-adaptation values are shown in Panels B and D. The arrow in each panel shows the position in the receptive field which was stimulated at 2 Hz during the 60 seconds of adaptation on each trial. The adaptation-induced response decrements were restricted to the OFF response profile and spread over a relative small area of the receptive field. The ON responses did not change following adaptation even though the adapting stimulus flashed both ON and OFF in the center of the receptive field.

Figure 12 caption
The aftereffects in cell su306 (see Figure 12) were restricted to the cell's OFF responses. Although the ON and OFF response profiles are overlapping and the peaks in these two profiles are at the same location, prolonged stimulation at this location resulted in response decrements in the OFF profile but no change in the ON profile. However, the complex cell su11 displayed adaptation effects which were limited to the ON response profile (see Figure 13). This cell gave primarily ON responses to flashed stimuli with a relatively weak OFF response. The OFF response profile largely overlapped the ON response zone and was, of course, stimulated during the adaptation period; however, the adaptation resulted in a very localized decrease in the ON responses while the OFF response profile showed no change in responses.

Both the cells in Figures 12 and 13 showed adaptation effects which were restricted to the profile (OFF or ON respectively) which was most responsive to stimulation suggesting a threshold response level for adaptation to occur. However the cell in Figure 14 responded equally well to stimulus onset and offset but showed adaptation effects only in the OFF response profile. The ON response profile showed a general increase in responsivity while the OFF response profile showed a highly asymmetric response decrement profile which was related to the direction selectivity of the cell. Receptive field positions to the right of the point of adaptation and on the preferred direction side were strongly adapted while positions equidistant but on the nonpreferred direction side showed increased responsivity. This was the most striking example of the asymmetry of adaptation effects related to direction selectivity observed in complex cells in these experiments.
The pre- and post-adaptation receptive field profiles for the ON and OFF responses of a typical complex cell (su11), which displayed adaptation effects in the ON profile only, are shown in panels A and C (respectively). Solid black lines represent the total number (in 32 repetitions) of pre-adaptation responses at each of the 15 points in the receptive field while the shaded grey lines show the post-adaptation responses at these same receptive field positions. The difference between the pre- and post-adaptation values are shown in Panels B and D. The arrow in each panel shows the position in the receptive field which was stimulated at 2 Hz during the 60 seconds of adaptation on each trial. The adaptation-induced response decrements were restricted to the ON response profile and spread over a relatively small area of the receptive field. The OFF responses displayed small variations in responsivity at various points in the receptive field these changes were small relative to the changes in the ON profile.
Number of stimulus offset spikes in 32 sweeps

Number of stimulus onset spikes in 32 sweeps

Change in number of stimulus offset spikes

Change in number of stimulus onset spikes
The pre- and post-adaptation receptive field profiles for the ON and OFF responses of a typical complex cell (su401), which displayed adaptation effects in the OFF profile only, are shown in panels A and C (respectively). Solid black lines represent the total number (in 32 repetitions) of pre-adaptation responses at each of the 15 points in the receptive field while the shaded grey lines show the post-adaptation responses at these same receptive field positions. The difference between the pre- and post-adaptation values are shown in Panels B and D. The arrow in each panel shows the position in the receptive field which was stimulated at 2 Hz during the 60 seconds of adaptation on each trial. The adaptation-induced response decrements were restricted to the OFF response profile and spread over a relatively small area of the receptive field in the preferred direction. Facilitation of responses were observed at position in the receptive field adjacent and in the nonpreferred direction to the point of adaptation. The ON response profile was characterized by small increases in responsivity at various points in the receptive field.
The spatial spread of adaptation in complex cells

As with simple cells (see chapter 2), the spread of adaptation across the receptive field was quantified using the standard deviation \( (s_2) \) of the best Gaussian curve fit to the response decrement profile for each cell (see Figure 3F). The results of this analysis revealed that the spread of adaptation fell along a continuum with values of \( s_2 \) larger than was observed for simple cells. The size of the receptive field was quantified using the standard deviation \( (s_1) \) of the best Gaussian curve fit to the pre-adaptation response profile (On + OFF) and then compared the size of the receptive field \( (s_1) \) with the spread of adaptation \( (s_2) \) by taking a ratio \( (R_s = s_1/s_2) \) for each cell. Thus adaptation spreading throughout an entire RF would be represented by \( R_s = 1 \), while adaptation spreading through only 1/2 would yield \( R_s = 2 \). Figure 15 A shows the frequency distribution of these ratios. Like simple cells, the frequency distribution of the ratio of the spread of adaptation to the size of the receptive field indicated three separate groups of cells; however, the ratios for complex cells were slightly higher than was observed for simple cells. The first group of cells (black bars) has a mean ratio of \( \overline{R_s} = 1.31 \) indicating that the adaptation encompasses the entire receptive field. The second group (white bars) had a larger mean ratio \( \overline{R_s} = 2.9 \) indicating that the adaptation spreads through approximately 1/3 of the receptive field. The final group (grey bars) had a mean ratio of \( \overline{R_s} = 4.53 \) indicating still more localized adaptation. As with simple cells, this method of cell classification decreased the variability associated with the linear regression (see Figure 15B). The correlation coefficient for the entire group of cells was \( R^2 = 0.44 \) while the correlation coefficients for the groups of cells defined by \( R_s \) were between 0.89 and 1.0. Since wavelength information was obtained for only a small number of complex cells a comparison of the spread of adaptation to the wavelength of the cell was not possible.
Panel A shows a frequency distribution (N=22) of the ratio of the size of the receptive field prior to adaptation to the size of the adaptation effect for all cells. The size of the receptive field subregion was defined as the standard deviation (s₁) of the best Gaussian curve fit to the sum of the ON and OFF response profiles. The size of the adaptation effect was defined as the standard deviation (s₂) of the best Gaussian fit to the adaptation-induced changes in responsivity for the subregion adapted. A ratio of \( R_S = s_1/s_2 = 1 \) indicates that the adaptation effects spread throughout the receptive field subregion. An \( R_S = 2 \) indicates that the adaptation effects spread through only 1/2 the subregion. Panel A shows that the population of complex cells falls into three significantly distinct groups based on the values of \( R_S \). Adaptation at one receptive field position can spread throughout the subregion (\( R_S \) between 1.0 and 2.0), or through 1/3 or 1/4 of the subregion. Panel B shows a scatterplot of the size of the receptive field plotted against the spread of adaptation across the receptive field for each group described above. Black squares represent the group of cells in Panel A which had \( R_S \) ratios less than 2.0. White circles and grey triangles represent the medium spread group (\( R_S = 2.9 \)) and the small spread group (\( R_S = 4.53 \)).
The same normalization procedure used for the simple cells (see Figure 6) was employed for complex cells to allow us to average the adaptation effects at fixed distances from the point of adaptation. Unlike simple cells, the effects of prolonged stimulation on the ON and OFF receptive field profiles were analyzed separately as they often displayed different degrees of adaptation in individual cells. The RFPs of each cell were converted into distance from the point of adaptation in units of S1 (standard deviations of the Gaussian Fit). Each cell's response profile was subjected to a linear interpolation yielding 150 points from the original 15 RFPs. The mean percent change in the responses at the point of adaptation and at 0.25s intervals could then be averaged.

Figure 16 shows the mean adaptation-induced response decrements for the entire population of complex cells. Equidistant points were averaged and plotted against the distance from the point of adaptation both as positive and negative x values to demonstrate the spread of adaptation around the point of adaptation. Error bars indicate the standard error of the mean. The response decrements which reached significance (criterion p<0.05) in a one group two tailed students T-test are indicated by an asterisk. Panel A shows the mean changes in the ON responses while panel B shows the mean changes in the OFF responses. The response decrements were strongest at the point of adaptation which showed a 30.25 \% drop in responses following adaptation. The adaptation effects decreased as the distance from the point of adaptation increased until at approximately 2 s distant the adaptation effects were negligible. The response decrements were significantly different from zero at the point of adaptation and within 1s in the ON response profiles (panel A). The OFF response profile showed approximately the same spread of adaptation but the adaptation-induced response decrements were much weaker at the point of adaptation.
The mean adaptation-induced percent change in response (N=22) is plotted against the distance from the point of adaptation in units of $s_1$ (receptive field size) for the ON and the OFF response profiles (panels A and B respectively). The RFPs of each cell were converted to distance from the point of adaptation in standard deviations (see Fig. 10) and the adaptation profile for each cell was subjected to a linear interpolation so that means could be taken at fixed distances from the point of adaptation. A mean percent change in response was obtained for the point of adaptation and for 0.25 s points distant. Equidistant RFPs were pooled and displayed symmetrically around the point of adaptation. An asterisk indicates a receptive field position for which the adaptation-induced change in responsivity was significantly different from zero (at $p<0.05$). Panel C shows the response decrement profiles for the ON and OFF profiles superimposed. The response decrement scores were normalized to the percent maximum decrement for the ON and OFF profiles separately.

Figure 16 caption

The mean adaptation-induced percent change in response (N=22) is plotted against the distance from the point of adaptation in units of $s_1$ (receptive field size) for the ON and the OFF response profiles (panels A and B respectively). The RFPs of each cell were converted to distance from the point of adaptation in standard deviations (see Fig. 10) and the adaptation profile for each cell was subjected to a linear interpolation so that means could be taken at fixed distances from the point of adaptation. A mean percent change in response was obtained for the point of adaptation and for 0.25 s points distant. Equidistant RFPs were pooled and displayed symmetrically around the point of adaptation. An asterisk indicates a receptive field position for which the adaptation-induced change in responsivity was significantly different from zero (at $p<0.05$). Panel C shows the response decrement profiles for the ON and OFF profiles superimposed. The response decrement scores were normalized to the percent maximum decrement for the ON and OFF profiles separately.
The percent of maximal decrement in responsivity (32 trials)

Distance from the point of adaptation (s)

The mean percent change in responsivity (32 trials)

The mean percent change in responsivity (32 trials)
The adaptation effects were similar for ON and OFF responses between 0.5 s and 1.25 s but were larger for the ON responses between 0 and 0.5s. In addition, the changes between 1.25 s and 4 s were negative for the ON responses but were positive for the OFF responses indicating a general decrease in the cells responses to stimulus onset and a general increase in response to stimulus offset at RFPs distant from the center of the receptive field. Panel C shows the response decrements for the ON and OFF profiles normalized so that we could directly compare the spread of adaptation in the ON and OFF receptive field profiles. The response decrements at each point in the ON receptive field profile were divided by 30.25 and multiplied by 100%. The OFF response decrements were divided by 20.18 and multiplied by 100%. The spread of adaptation in the ON and OFF profiles was not different when the profiles are normalized for the magnitude of the response decrements.

Figure 17 shows the results of analyzing the data of Figure 16 such that the line-weighting function for each cell was aligned based on the cell's direction selectivity. To do this the orientation of each cell's receptive field was rotated such that the preferred direction of stimulus motion of each cell was aligned with all other cells in the population. The mean percent change in response at the point of adaptation and 0.25 s points distant were then averaged. RFPs with positive distances from the point of adaptation (to the right of zero) would be stimulated by a bar of light originating at the point of adaptation and moving in each cell's preferred direction. RFPs with negative distances from the point of adaptation (to the left of zero) would be stimulated by a bar of light beginning at the point of adaptation and moving in the cell's nonpreferred direction. Figures 17 A and B show the spread of adaptation for ON and OFF response decrements (respectively) of all cells as a function of position corresponding to the unit's preferred and nonpreferred direction.
Figure 17 caption

The spread of the adaptation for ON (panel A) and OFF profiles (panel B) when the receptive fields for the cells have been aligned with respect to their preferred directions of motion (N=22). A bar of light moving across the receptive field in the cells preferred direction would pass RFP 0 s before passing positions to the right. A bar of light moving in the nonpreferred direction would pass RFP 0 s before passing through positions to the left of 0. The adaptation spread asymmetrically with larger declines in responsivity at preferred side RFPs than for equidistant points located on the nonpreferred side of the point of adaptation. Panel C shows the mean difference between the ON and OFF response decrement.
The mean on-off difference in the percent change in responsivity (32 trials)

The mean percent change in responsivity (32 trials)

The mean percent change in responsivity (32 trials)
Panels A and B show the directional asymmetry of the spread of the adaptation across the receptive fields of complex cells for the ON and OFF receptive field profiles respectively (N=22). Mean response decrement scores for RFPs in the preferred direction were subtracted from scores in the nonpreferred direction for points equidistant from the point of adaptation (error bars indicate standard error). Difference scores less than zero represent larger response decrements for RFPs in the preferred direction than in the nonpreferred direction. An asterisk indicates a receptive field position at which the directional asymmetry (P spread - NP spread) was significantly different from zero (at p < .05). The adaptation of the ON profile spread asymmetrically and the directional asymmetry of the spread of adaptation was greatest at 0.5 s from the point of adaptation. Panel C shows the mean difference between the ON and OFF response asymmetry scores.
The difference between the mean directional asymmetry of the adaptation of the on and off receptive field profiles.

The mean directional asymmetry of the spread of adaptation (percent change).

The mean directional asymmetry of the spread of adaptation (percent change).
of motion. As in Figure 16, the greatest response decrement was at the point of adaptation where both the ON and OFF responses were significantly decreased. The spread of ON response adaptation was similar to the spread of adaptation for simple cells, with a marked asymmetry in the adaptation effects predicting weaker responses in the preferred direction. For the OFF responses, the adaptation profile appeared more symmetrical. The OFF response decrement profile showed a small asymmetry in the opposite direction with decreased responsivity at nonpreferred direction positions and facilitation at 2.0 s in the preferred direction. Panel C shows the difference between the response decrements of the ON and OFF receptive field profiles. Difference scores below zero indicate greater response decrements in the ON responses while scores above zero indicate greater decrements on the OFF profile. This method of analysis demonstrates the difference between the ON and the OFF response profiles in the asymmetry of the adaptation. The ON response profile shows greater adaptation effects at receptive field positions located on the preferred direction side of the point of adaptation. Although the magnitude of the OFF response decrements were less than the ON decrements, the adaptation spread more in the opposite direction from that shown in the ON response profile decrements. That is, the adaptation in the OFF response profile was greater at receptive field positions located on the nonpreferred direction side of the point of adaptation. This is illustrated by the dramatic shift in the sign of the difference scores to the left and right of zero in panel C.

As with simple cells, response decrement scores in the preferred direction for each individual cell were subtracted from scores in the nonpreferred direction for points equidistant from the point of adaptation. Mean directional asymmetry scores less than zero represent points in the adaptation profile at which there was more adaptation at points corresponding to preferred direction stimulation than
nonpreferred direction stimulation. Figure 18 A and B show the mean directional asymmetry for the ON and OFF response profiles (respectively) for all complex cells studied. Panel A shows that the greatest mean directional asymmetry in the ON response profiles was at 0.5 s from the point of adaptation. Directional asymmetry scores were negative (indicating greater adaptation of points on the preferred direction side) up to 3.25 s from the point of adaptation. The asymmetry scores for the OFF responses in panel B are strikingly dissimilar to the ON response scores in panel A. The OFF response profiles showed significant directional asymmetry at only one point in the receptive field—at 1.0 s from the point of adaptation. The asymmetry scores do get larger at distances greater than 2 s but the variability also increases and at these distances the sample size is reduced. Panel C shows the mean difference between the ON and the OFF asymmetry scores. The asymmetry scores were greater in the ON response profiles than in the OFF except at positions distant from the point of adaptation.

Discussion

The results reported here show that adaptation occurs following prolonged stimulation of a restricted area within a cortical cell's receptive field. This confirms the results of Kulikowski et al. (1981) who demonstrated adaptation of simple cell subregions using a stimulus with a sawtooth luminance profile which was swept through the receptive field inducing either On or OFF responses. I have gone beyond this, however, in showing that the adaptation does not necessarily spread across an entire ON or OFF subregion. Rather, it can be restricted to a small area surrounding the point in the receptive field stimulated during adaptation. Adaptation is, in general, strongest at the point of prolonged stimulation, and decreases with
distance; however, the magnitude of the response decrement and the spread of adaptation over the receptive field can be different for each cell.

*Simple cells*

The spread of adaptation was not related to the overall size of the receptive field, as might be expected, but was instead a simple fraction of the size of the receptive field subregion in which the prolonged stimulation was presented. The cells could also be categorized by the relationship between the spatial wavelength of the cell (as determined by the relative positions of the ON and OFF subregions) and the spread of adaptation. However, the spatial wavelength (a measure relating to the entire receptive field) and the size of the receptive field in degrees of visual angle were both poorly correlated with the spread of adaptation. The size of the adapted subregion was significantly correlated with the spread of adaptation. The significance of this relationship and the low correlations between the spread of adaptation and measures of the size of the entire receptive field indicate that the ON and OFF subregions can be functionally independent. Prolonged stimulation within an ON region will induce adaptation effects which are typically confined to that ON region. In some cases there is an interaction between the ON and OFF subregions such that adaptation in an ON subregion will influence the responses in the neighboring OFF subregion. The sign of the adaptation-induced changes in responsivity in the non-adapted subregion will depend on the type of interactions between the antagonistic subregions. For example, the profile shape of an ON region could influence the profile shape of an adjacent OFF region through inhibition. Adaptation which alters the responses at some positions in the ON region would indirectly alter the OFF responses. This type of subregion interaction was infrequent in our population of simple cells. This would explain the weaker relationship between the spatial wavelength of the receptive field and the spread of adaptation.
across the receptive field. The spatial wavelength is influenced more by the spatial positions of the receptive field subregions than is the size of each subregion.

*Complex cells*

Complex cells showed position specific adaptation within their receptive fields in a manner similar to that of simple cells. Prolonged stimulation at one receptive field position produced response decrements at that position and at nearby positions. The spread of adaptation occurred over a larger spatial scale in complex cells due to the slightly larger Gaussian envelope of the receptive fields in these cells. The magnitudes of the response decrements were also similar to that observed in the simple cells. In simple cells there are subtle interactions between the ON and the OFF subregions which can reduce the size of the gaussian envelope for one or both subregions. In complex cells the interactions are within the subregions and do not appear to affect the size of the receptive field. As in simple cells the size of the stimulus was not significantly correlated with the spread of adaptation in complex cells.

*The spatial spread of adaptation*

Adaptation-induced response decrements are not observed throughout the receptive field but are localized to the region of prolonged stimulation which supports the hypothesis that adaptation does not result from a general fatigue but a more local mechanism. There is a large reduction in responsivity at the point of adaptation and the spread of this adaptation across the receptive field is limited. Although the spread of adaptation is different for each cell the adaptation does not typically spread beyond the borders of the subregion stimulated. In other words, in simple cells adaptation in a receptive field ON area will remain within that subregion and will not encroach into neighboring OFF regions. Furthermore, the
degree to which the adaptation spreads from the epicenter is closely related to the
type of the subregion stimulated (and to some degree the spatial wavelength of the
cell) and not strongly dependant upon the size of the bar of light used during
stimulation. In simple cells, three subpopulations emerged when we examined the
ratio of the size of the subregion to the spread of adaptation across the receptive
field. In the first group \((R_5 \leq 1)\) the adaptation spreads throughout the subregion
causing a reduced response at all RFPs within that subregion. This may reflect the
lack of segregation of afferent inputs implying that individual geniculate afferents
may themselves be the major contributor to the receptive field subregion.
Alternatively the afferent inputs may be segregated into distinct subunits but because
of extensive lateral excitatory connections the population of subunits comprising the
receptive field subregion becomes adapted along with the point of adaptation. In
these neurons the adaptation cannot represent a nonspecific depression of
postsynaptic cell responsivity because the adaptation-induced response decrements
were confined to the adapted subregion and were not observed in the unit's non-
stimulated antagonistic subregions. The other cell groups in which the adaptation
effects were even more spatially restricted may have extensive segregation of the
afferent inputs or less extensive lateral excitatory connections between the subunits
of the receptive field.

Adaptation with a single bar at one RFP could simultaneously decrease
excitatory lateral interactions and increase inhibitory interactions. The increased
inhibition at some RFPs a particular distance from the site of adaptation could
actually protect those positions from adaptation effects and therefore the spread of
adaptation would be restricted. However, if the prolonged stimulation reduced
inhibition, then more of the cells' receptive field would be influenced by lateral
excitatory connections and the spread of adaptation could be increased.

*Directional asymmetry of adaptation*
Prolonged stimulation at a single receptive field position induced adaptation of responses at adjacent RFPs in a direction specific manner. Each receptive field can be divided into two separate sub-fields (preferred direction side and nonpreferred direction side) with the point of adaptation located at the border between them (see Figure 8). RFPs located on the preferred direction side of the point of adaptation showed significantly more adaptation-induced response decrements than did RFPs equally distant but located on the nonpreferred direction side. Furthermore, there were significant increases in the responsivity of a number of RFPs on the nonpreferred direction side. The directional asymmetry of the spread of adaptation was greatest at 0.2 \( \lambda \) from the point of adaptation in simple cells suggesting that excitatory and inhibitory interactions within the receptive fields of simple cells are at their maximum at around 0.2 \( \lambda \). This position for maximal directional asymmetry of adaptation is interesting in light of the results of Baker and Cynader (1986). They showed that the optimal spatial separation (\( D_{opt} \)) for two bar stimuli presented in apparent motion within the receptive field of direction-selective simple cells was related to the spatial wavelength of the cell and was close to 0.2 \( \lambda \). One way to relate their findings to the present results would be to suggest that stimulation at the point of adaptation was also maximally stimulating the RFPs 0.2 \( \lambda \) distant in the preferred direction via lateral excitatory connections and inhibiting the corresponding positions 0.2 \( \lambda \) distant in the nonpreferred direction via lateral inhibitory connections. Following adaptation the strength of these facilitatory or inhibitory effects would be reduced, resulting in weakened responses on the preferred direction side and paradoxical increases on the nonpreferred direction side.

Facilitation was not observed very close to the point of adaptation. Prolonged stimulation at the point of adaptation would result in response decrements very close to that point if the receptive field afferent inputs were overlapping. Alternatively, the
bidirectional spread of adaptation over such a short distance could result from a finite region of lateral excitatory interactions which extend in both the preferred and the nonpreferred directions. Stimulation at the point of adaptation may produce inhibition at RFPs further from the point of adaptation and in the nonpreferred direction. There is strong evidence supporting both the short excitatory and the longer inhibitory interactions (Hess, Negishi, & Creutzfeldt, 1975). Furthermore, the asymmetry of lateral inhibition within a visual cortical simple cell's receptive field has been proposed as a mechanism for direction selectivity (Bishop et al., 1974; Emerson & Gerstein, 1977; Ganz, 1984; Ganz & Felder, 1984; Goodwin et al., 1975).

Prolonged stimulation at a single receptive field position appears to induce response decrements within a range of excitatory interactions while simultaneously adapting inhibitory interactions in the nonpreferred direction. This would be reflected by an increase in the excitability of those receptive field areas which have been released from inhibition. This would also account for the findings of Marlin et. al. (Marlin et al., 1988) and others who found enhanced preferred direction responses in simple cells following prolonged unidirectional motion in a cell's nonpreferred direction. If adaptation in a simple cell's nonpreferred direction selectively adapts intrinsic inhibitory connections which reduce a neuron's response to motion in the nonpreferred direction, then we would expect to observe an increase in nonpreferred direction responses but no increase in preferred direction responses. If, however, nonpreferred direction adaptation adapts a general inhibitory process which underlies direction selectivity as well as controlling the gain of the cells evoked responses and spontaneous activity, then nonpreferred direction adaptation could produce an overall increase in responsivity while simultaneously decreasing nonpreferred responses. The degree to which the cell displays adaptation-induced response decrements or increments could depend on the relative amounts of inhibition and facilitation stimulated by the adaptation process. The directional asymmetry of position specific
adaptation suggests that these two processes may adapt independently.

*On verses Off adaptation in complex cells*

The adaptation effects were observed for both the ON and the OFF responses but could be restricted to only one of these responses in individual cells despite completely overlapping receptive field profiles. Although the ON and OFF receptive field profiles were largely overlapping, the magnitude of the ON and OFF responses could be extremely different. In those cells with specific ON or OFF response adaptation, the pre-adaptation responsivity to that stimulus was typically much higher than the nonadapted stimulus (4/6 cells). That is, a cell with a large ON response and a relatively weak OFF response would show ON response adaptation but not OFF response adaptation. This unipolar adaptation might result from a response dependent spike frequency adaptation or some other response related mechanism directly related to neuronal activity (see Part III). However this was not necessarily the case. The cell shown in Figure 14, for instance, had equal ON and OFF responses before adaptation but showed strong unipolar adaptation in the OFF response profile. It is clear that some additional property determines the adaptation of ON and OFF response profiles in complex cells that goes beyond a response based mechanism.

In general, ON responses displayed stronger adaptation-induced response decrements which suggests that the on channel from the retina to the visual cortex is more susceptible to adaptation than the off channel. It should be noted, however, that all our experiments used light slits instead of dark bars as stimuli. Recent experiments have demonstrated differences between the neurotransmitter receptors used by the ON and OFF channels (Chen & Linsenmeier, 1989; Schiller, 1990). Schiller (1990) recently showed that the glutaminergic antagonist amino-4-phosphonobutyrate
(APB) injected into the rhesus monkey vitreous humor eliminated the ON responses of geniculate and cortical neurons but did not change the OFF responses. Furthermore, interactions between ON and OFF channels do not form the center-surround receptive fields of LGN cells but do converge on the receptive fields of complex cells in the visual cortex. It is therefore possible that the glutaminergic pathway within the visual cortex for ON responses is more susceptible to adaptation than the OFF pathway. There is some evidence that in certain cells the activation of non-NMDA glutamate receptors prevents the sAHP induced by baclofen (Rovira, Gho, & Ben-Ari, 1990) (see Chapter 7 for a discussion of these mechanisms of adaptation).

In addition to differences in the strength of the adaptation between the ON and the OFF response profiles in the complex cell receptive fields, there were also differences in the asymmetric spread of adaptation. The directional asymmetry was much stronger in the ON response profiles than in the OFF profiles. However, the direction of the asymmetry was different for the ON and OFF profiles. For the ON profiles the adaptation was strongest in the preferred direction while the OFF adaptation was slightly stronger in the nonpreferred direction. There may be interactions between the ON and OFF responses which give rise to direction selective facilitation or inhibition (see chapter 4). Prolonged stimulation at one receptive field position results in response decrements at receptive field positions connected to that point via lateral excitation. Those positions connected via lateral inhibition would display facilitation following prolonged stimulation. A pattern of connections which facilitate ON-ON interactions would result in very different types of adaptation than OFF-OFF, ON-OFF or OFF-ON interactions. ON-ON interactions would be characterized by primed receptive field subunits downstream (in the cells preferred direction) in the receptive field. The result of this priming could be an increase in the membrane potential towards the spike threshold via lateral excitatory connections and EPSPs. These subthreshold EPSPs could
themselves induce adaptation at sites distant from the point of adaptation.

The locus of adaptation

It is necessary to rule out peripheral causes which may contribute to the cortical response decrements observed after prolonged stimulation. It is possible that the reduction in responsivity, or at least part of it, results from photoreceptor bleaching or adaptation of either retinal or geniculate neurons. However, the following evidence suggests the adaptation is occurring within the striate cortex: 1) Psychophysical studies on pattern adaptation aftereffects suggest that pattern aftereffects originate at a level higher than the lateral geniculate in the visual pathway. These aftereffects demonstrate a specificity for the stimulus parameters present in the adapting stimulus such as spatial frequency, orientation or direction of stimulus motion-parameters which are present in the visual cortex but not in the LGN. In neurophysiological studies, the adaptation is also found to be specific to particular cortical properties such as spatial frequency (Maffei et al., 1973; Movshon, Bonds, & Lennie, 1980; Saul & Cynader, 1988; Saul & Cynader, 1989a) orientation (Saul & Cynader, 1989a), and direction selectivity (Hammond, Mouat, & Smith, 1985; Hammond, Mouat, & Smith, 1986; Maffei et al., 1973; Marlin & Cynader, 1986; Marlin et al., 1987; Marlin et al., 1988; Movshon et al., 1980; Petersen et al., 1985; Saul & Cynader, 1988; von der Heydt, Hanny, & Adorjani, 1978); 2) a number of investigators (Movshon et al., 1980; Saul & Cynader, 1989a) have tried adapting LGN cells using the stimulus parameters optimal for cortical cells and have found them to be relatively resistant to adaptation (see Chapter 3 for exceptions); 3) In psychophysical experiments, monocularly induced motion and spatial frequency adaptation aftereffects also show interocular transfer (Anderson & Movshon, 1989; Cogan, 1987; Favreau, 1978; Favreau & Cavanagh, 1984; Mitchell et al., 1975; O'Shea & Crassini, 1981; Selby & Woodhouse, 1981; Smith, 1983; Tyler & Nakayama, 1980). In these experiments it was shown that prolonged monocular stimulation reduced the
responses in the adapted as well as the nonadapted eye. The adaptation effects are generally believed to be the result of adaptation of cortical neurons. Although there is limited evidence for binocular interactions within the LGN (Christen & Mower, 1987; Guido, Tumosa, & Spear, 1989; McCall, Spear, Crabtree, & Kornguth, 1987; Xue, Ramoa, Carney, & Freeman, 1987), the first site in the geniculo-striate pathway containing a high proportion of binocularly driven cells is in the striate cortex (Casanova, Freeman, & Nordmann, 1989; Elberger, 1989; Hubel & Wiesel, 1962; Ohzawa & Freeman, 1986a; Ohzawa & Freeman, 1986b; Paradiso et al., 1989; Tootell, Hamilton, Silverman, & Switkes, 1988; von Grunau, 1979). Interocular transfer of adaptation has been demonstrated in many binocular neurons in area 17 (Hammond & Mouat, 1988; Maffei et al., 1986; Marlin et al., 1987). In the results reported here, interocular transfer was demonstrated in three binocular simple cells using the same stimulus parameters as the other 22 simple cells in our population. Although this does not prove that the adaptation observed in the monocularly studied cases is cortical, it does show that (in at least those binocular cells) the adaptation involves binocular processing. Furthermore, the spread of adaptation in the striate cortex is related to the direction selectivity of the cells. Direction selectivity is largely a cortical property, and thus the directional asymmetry of the spread of adaptation is further evidence for a cortical locus for the position specific adaptation reported here.

Despite these effects it can still be argued that adaptation observed in the visual cortex originates in the LGN and is simply reflected in the cortical cells. The interocular transfer and feature specificity of adaptation could result from a reduction in monocular geniculate inputs to the cortical mechanisms for binocularity or feature detection (Anderson & Movshon, 1989; Cogan, 1987). Neurophysiological attempts to produce contrast adaptation in the LGN have all yielded similar results, indicating that LGN cells do not show contrast adaptation to drifting high contrast sine-wave gratings (Movshon et al., 1980; Ohzawa et al., 1982; Ohzawa et al., 1985; Sclar, 1987; Sclar,
Ohzawa, & Freeman, 1985). These studies all employed large, whole field drifting sine wave gratings as adapting stimuli which have been shown to produce strong adaptation in cortical neurons (Albrecht et al., 1984; DeBruyn & Bonds, 1986; Hammond & Mouat, 1988; Hammond et al., 1988; Hammond et al., 1985; Hammond et al., 1986; Hammond et al., 1989; Kulikowski et al., 1981; Maddess et al., 1988; Maffei et al., 1986; Maffei et al., 1973; Marlin & Cynader, 1986; Marlin et al., 1989; Marlin et al., 1987; Marlin et al., 1988; Movshon et al., 1980; Ohzawa et al., 1982; Ohzawa et al., 1985; Petersen et al., 1985; Saul & Cynader, 1988; Saul & Cynader, 1989a; Saul & Cynader, 1989b; Sclar, 1987; Sclar et al., 1989; Sclar et al., 1985; Vautin & Berkley, 1977; Vidyasagar, 1990; von der Heydt et al., 1978). However, LGN cells have concentric center surround opponent receptive fields and are therefore not optimally stimulated by whole field stimulation. Furthermore, the temporal parameters of responses in the LGN are different from those of the striate cortex. Cells in the LGN can entrain to stimuli whose contrast is modulated at rates of up to 50 Hz while cells in area 17 of the the striate cortex often fail above 7 Hz (Ferster & Lindstrom, 1985a; Ferster & Lindstrom, 1985b; Jones & Berkley, 1983). LGN cells have been described as firing continuously to sinusoidally modulated stationary gratings (Virsu & Lee, 1983). To be truly convinced that the adaptation effects observed in chapter 2 were cortical in origin, cells in the LGN and geniculate afferents recorded in the striate cortex were tested for adaptation to stimuli presented in the same manner as that used for cortical cells in chapter 2 (at 2 Hz). A number of geniculate cells were also tested with stimuli which were presented at higher flicker rates (up to 20 Hz).
Chapter 3

Adaptation Of Cells In The Dorsal Lateral Geniculate Nucleus

Methods

Surgical Procedures and Physiologic Recording

The adaptation of LGN cells and afferents recorded in the visual cortex was investigated in 5 geniculate afferents recorded in area 17 and in 5 geniculate cells recorded in the LGN. The general methods for recording single unit activity from area 17 of acutely prepared anesthetized cats have been described in detail in chapter 1. Geniculate afferents were characterized by small receptive fields with center-surround antagonism. They responded to small light or dark spots and did not display elongated receptive fields. Furthermore the geniculate afferents in area 17 would respond to whole field flicker at rates above 10 Hz.

To record from cells within the LGN an additional craniotomy was made at stereotaxic coordinates A5;L9.5. The electrode was lowered manually 10 mm from the cortical surface and advanced to about 14 mm from the cortical surface in 100 μ steps using the microdrive while sampling the responses of cells in the area of the electrode to whole field flashed stimuli. The surface of the LGN was marked by an increase in the number of cells responding to visual stimuli and by a clear monocular response which was well localized at a particular point in the visual field. The electrode was then advanced in 25 μ steps until single LGN cells could be isolated. The cell was determined to be either ON or OFF centered and this determined the choice of a spot or an annulus for subsequent stimulation. All stimuli were presented monocularly.

Adaptation experiments consisted of a number of stimulus presentations 2 seconds apart to determine the baseline firing rate. The stimulus was then presented
at a higher frequency (2-20 Hz square wave modulation) for at least 30 seconds and up to 90 seconds. Immediately following the last adaptation trial the stimulus was presented a number of times at a rate of 0.5 Hz as in the pre-adaptation trials. The entire cycle was repeated 3-8 times and a 60 sec recovery period separated the end of the post-adaptation testing and the pre-adaptation baseline periods. The duration of the stimulus was constant within each experiment.

**Results**

Although one geniculate cell showed some adaptation to 2 Hz stimulation the magnitude of the effects were small. The remaining geniculate cells showed no appreciable adaptation at 2 Hz and many did not adapt at 5 Hz. All LGN cells showed adaptation to 10 Hz with the decline in responsivity occurring rapidly (time constants 2-6 seconds). The time constants for the adaptation were not systematically related to the number of stimuli presented (see Table 1).

The effects of adaptation at 2 Hz for 3 typical geniculate afférents (2 recorded in cortical layer 4 and 1 recorded in the white matter beneath layer 6 of the striate cortex) and a simple cell recorded in the same electrode penetration which was located within 100 µ of the geniculate afférents in layer 4 are shown in Figure 19. The geniculate afférents had receptive fields within 5 ° of the area centralis and responded preferentially to stimulus onset. No attempt was made to classify the afférents as representing X or Y geniculate cells. Each of the geniculate afférents shown in Figure 19 showed high variability during the baseline period and although the variability decreases during the adaptation phase there is no appreciable decline in the magnitude of the response over time. Similarly there is no change during the 90 sec recovery period. In other words, the LGN afférents do not show response magnitude adaptation to stimuli presented at a rate of 2 Hz. Compare these results to those of a simple cell recorded near the LGN afférent fibers (Figure 19 D). This
Table 1.

The time constants (τ) of adaptation for each geniculate afferent and geniculate cell in both seconds and trials (number of stimuli). For each cell the responses during adaptation were fit with a single exponential curve. The tau (τ) for the simplex curve fit was either the time in seconds from the initiation of adaptation or the trial number. The term NA indicates that the experiment was not done on this cell and therefore this analysis is not applicable.
Table 1  
Adaptation time constant (τau)

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<tr>
<th>cell</th>
<th>τ in seconds</th>
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<th>τ in number of stimuli</th>
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<tr>
<td></td>
<td>5hz</td>
<td>10hz</td>
<td></td>
<td>5hz</td>
</tr>
<tr>
<td>j4 af 1</td>
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<td></td>
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Panels A-C show the effects of 0.5 Hz (□) and 2 Hz (●) stimulation on three geniculate afferents recorded in area 17 of the cat visual cortex. Panel D show the effects of the same rates of stimulation on a layer 4 simple cell recorded in the same penetration. The number of spikes recorded from the fiber during the four repetitions is shown on the ordinate while the abscissa displays the time in seconds from the beginning of each cycle. Notice that the scale on the x-axis changes during the pre-adaptation, adaptation, and post-adaptation phases of the cycle for each panel. The receptive field was stimulated at a rate of 0.5 Hz for the pre and post-adaptation periods (all panels). Neither 0.5 nor 2 Hz stimulation reduced the responsivity of the geniculate afferents while 2 Hz stimulation resulted in pronounced adaptation of responses in the simple cell (panel D). The adaptation effects decayed within 30 sec following the cessation of the 2 Hz stimulation in this simple cell.
A

Preadaptation (0.5 Hz)

B

Adaptation 2 Hz

C

Postadaptation (0.5 Hz)

D

The total number of geniculate afferent spikes in 4 sweeps

Time in seconds

95
Panels A-C show the effects of 0.5 Hz (□) and 5 Hz (●) stimulation on three geniculate afferents recorded in area 17 of the cat visual cortex. Panel D shows the effects of the same rates of stimulation on a layer 4 simple cell recorded in the same penetration. The number of spikes recorded from the fibers during the four repetitions is shown on the ordinate while the abscissa displays the time in seconds from the beginning of each cycle. Notice that the scale on the x-axis changes during the pre-adaptation, adaptation, and post-adaptation phases of the cycle for each panel. The receptive field was stimulated at a rate of 0.5 Hz for the pre- and post-adaptation periods (all panels). Stimulation at 5 Hz induced adaptation of responses of the geniculate afferents and resulted in reduced responsivity in the simple cell (panel D). The adaptation effects decayed within 30 sec following the cessation of the 5 Hz stimulation in geniculate afferents. The immediate increase in firing following the end of the 5 Hz stimulation in the simple cells suggests that the decrease during the 5 Hz was not truly adaptation but related to the temporal frequency tuning of the cell.
simple cell showed less variability during baseline and a dramatic exponential decline in responsivity during the 2 Hz stimulation. Notice that during the recovery phase the responsivity to stimulation slowly recovers over 30 seconds suggesting a true adaptation phenomenon rather than a decrease in responding due to an inability to phase lock with the stimulus presentation which can often occur at higher temporal frequencies (see Fig. 20 D for an example of this). As with 2 Hz stimulation, the variability in the responses of these geniculate afferents decreased during 5 Hz stimulation (see Figure 20). In addition there was an initial increase in the response when the rate of stimulation changed from 0.5 Hz to 5 Hz. This increase was not observed for 2 Hz stimulation for these same cells. Following the initial increase in responsivity there was a rapid decline in responsivity during the adaptation period to an asymptotic level of responding which was approximately 50% of the initial 5 Hz rate. Although the response rate during the last adaptation trial was at the level of the pre-adaptation baseline in panels A-C, the firing level during the first recovery trial was much lower than either the baseline rate or the adaptation asymptote. There were 2 seconds between the last adaptation trial and the first recovery trial which would suggest that the cell should fire as if the stimulus had been presented at 0.5 Hz. Since the firing rates during the recovery phase increased exponentially over time and had a time constants of between 5 and 15 seconds, it is likely that a single adaptation process evoked by the 5 Hz stimulation decreased the firing rates regardless of the rate of stimulation. This was not the case for the simple cell because the responsivity decreased immediately following the onset of 5 Hz stimulation and there was an immediate recovery when the stimulation rate dropped to 0.5 Hz (see Figure 20 D). This suggests that the cortical cell was not adapted, but that its temporal frequency tuning was low pass and it simply did not respond to high stimulation rates.
The frequency dependence of adaptation is shown for a geniculate afferent (GA 2.1) recorded in area 17. The number of spikes recorded from the fiber during the four repetitions is shown on the ordinate while the abscissa displays the time in seconds from the beginning of each cycle. Notice that the scale on the x-axis changes during the pre-adaptation, adaptation, and post-adaptation phases of the cycle for each panel. The receptive field was stimulated at a rate of 0.5 Hz for the pre and post-adaptation periods (all panels). Panel A shows the responses do not adapt when the receptive field is stimulated at 2 Hz. Panel B shows moderate adaptation to stimulation at 5 Hz while panel C shows substantial adaptation to 10 Hz stimulation. Panel D shows the effects of 20 Hz stimulation on the responses of the cell. While there is adaptation during the 20 Hz stimulation there is also an increase in the variability of the magnitude of the response.
The effects of 2, 5 and 10 Hz stimulation on the responses of a cell recorded in layer A1 of the lateral geniculate nucleus (cell LGN2 A1-1). The number of spikes recorded from the cell during the five repetitions is shown on the ordinate while the abscissa displays the time in seconds from the beginning of each cycle. Notice that the scale on the x-axis changes during the pre-adaptation, adaptation, and post-adaptation phases of the cycle for each panel. The receptive field was stimulated at a rate of 0.5 Hz for the pre and post-adaptation periods (all panels). Panel A shows the responses do not adapt when the receptive field is stimulated at 2 Hz. Stimulation at 2 Hz did not result in adaptation of responses (panel A) while 5 Hz (panel b) and 10 Hz stimulation rates resulted in an exponential decline in responsivity with time constants of 1.96 and 1.15 respectively. The recovery from adaptation was slower than the rate of adaptation.

Figure 22 caption

The effects of 2, 5 and 10 Hz stimulation on the responses of a cell recorded in layer A1 of the lateral geniculate nucleus (cell LGN2 A1-1). The number of spikes recorded from the cell during the five repetitions is shown on the ordinate while the abscissa displays the time in seconds from the beginning of each cycle. Notice that the scale on the x-axis changes during the pre-adaptation, adaptation, and post-adaptation phases of the cycle for each panel. The receptive field was stimulated at a rate of 0.5 Hz for the pre and post-adaptation periods (all panels). Panel A shows the responses do not adapt when the receptive field is stimulated at 2 Hz. Stimulation at 2 Hz did not result in adaptation of responses (panel A) while 5 Hz (panel b) and 10 Hz stimulation rates resulted in an exponential decline in responsivity with time constants of 1.96 and 1.15 respectively. The recovery from adaptation was slower than the rate of adaptation.
The effects of 2, 5 and 10 Hz stimulation on the responses of a cell recorded in layer A1 of the lateral geniculate nucleus (cell LGN3 A1-3). The number of spikes recorded from the cell during the five repetitions is shown on the ordinate while the abscissa displays the time in seconds from the beginning of each cycle. Notice that the scale on the x-axis changes during the pre-adaptation, adaptation, and post-adaptation phases of the cycle for each panel. The receptive field was stimulated at a rate of 0.5 Hz for the pre and post-adaptation periods (all panels). Panel A shows the responses initially increase and then decrease when the receptive field is stimulated at 2 Hz. The decline in responses during observed during 2 Hz stimulation is only 8% of the initial firing rate. Panel B shows the effects of 5 Hz stimulation on the responses of the cell. Although the responses to 0.5 Hz were much less with a stimulus duration of only 100 ms the onset of 5 Hz stimulation caused a large increase in the firing rate. The responses then decreased exponentially (T=16.6). The post-adaptation recovery phase shows that the adaptation is not temporal frequency specific because the firing rate to 0.5 Hz stimulation was also reduced and recovers slowly with a time constant of 14.7 sec. Panel C shows the effects of 10 Hz stimulation on the responses of the cell. The 50 ms stimulus duration resulted in increased variability of responsivity during the baseline. The onset of the 10 Hz stimulation rate doubled the responsivity. The responses then declined exponentially with a time constant of 3.03 sec.
LGN 3
layer a1
cell 3

A

0.5 Hz Preadapt  2 Hz Adapt  0.5 Hz Recovery

Number of spikes in 5 repetitions

B

0.5 Hz Preadapt  5 Hz Adapt  0.5 Hz Recovery

Number of spikes in 5 repetitions

C

0.5 Hz Preadapt  10 Hz Adapt  0.5 Hz Recovery

Number of spikes in 5 repetitions

Time in seconds
The effects of 2, 5 and 10 Hz stimulation on the responses of a cell recorded in layer A of the lateral geniculate nucleus (cell LGN3 A-1). The number of spikes recorded from the cell during the five repetitions is shown on the ordinate while the abscissa displays the time in seconds from the beginning of each cycle. Notice that the scale on the x-axis changes during the pre-adaptation, adaptation, and post-adaptation phases of the cycle for each panel. The receptive field was stimulated at a rate of 0.5 Hz for the pre and post-adaptation periods (all panels). There was no change in responsivity when the stimulus rate changed from 0.5 Hz to 2 Hz (panel A). Panel B shows the effects of 5 Hz stimulation on the responses of the cell. The responses decreased exponentially during the 5 Hz stimulation with a short time constant of adaptation ($T=1.05$). Panel C shows the effects of 10 Hz stimulation on the responses of the cell. The 50 ms stimulus duration resulted in increased variability of responsivity during the baseline and during adaptation to 10 Hz. Although the high variability made the exponential curve fits less reliable the effect is clearly a reduction in the mean firing rate over time.
A

LGN 3
layer a
cell 1

0.5 Hz Preadapt  2 Hz Preadapt  0.5 Hz Recovery

Number of spikes in 5 repetitions

Time in seconds

B

0.5 Hz Preadapt  2 Hz Preadapt  0.5 Hz Recovery

Number of spikes in 5 repetitions

Time in seconds

C

0.5 Hz Preadapt  2 Hz Preadapt  0.5 Hz Recovery

Number of spikes in 5 repetitions

Time in seconds
Figure 21 shows the responses of a geniculate afferent which showed a different threshold stimulation rate for induction of adaptation. Panel A shows that there was no adaptation to a 2 Hz adaptation stimulus while 5 Hz resulted in only minimal adaptation of the fiber (panel B). Stimulation at 10 Hz (panel C) proved optimal for this geniculate fiber (panel D).

Of the five cells recorded in the lateral geniculate nucleus only one cell showed adaptation to stimulation rates as low as 2 Hz. The cell was located in layer C of the LGN and showed W cell-like characteristics. This cell responded transiently to stimulus onset and stimulus offset was characterized by 2 distinct processes. Stimulus offset resulted in a very brief burst of spikes followed 300 ms later by a sustained OFF response. This cell did not respond well to short duration pulses of light and so the adaptation effects observed at 10 Hz are unclear.

Figures 22, 23 and 24 show the frequency dependent adaptation of three cells recorded in the lateral geniculate nucleus. The time constant of adaptation of the cell shown in Figure 22 was shorter for the 10 Hz adaptation than for the 5 Hz adaptation (1.15 & 1.96 seconds respectively). The time constant for 10 Hz adaptation was approximately half that of 5 Hz adaptation suggesting that adaptation might depend on the number of stimulus presentations. If the time constant is determined using trial number rather than time as the x in equation 19 then the number of stimuli required to reduce the response level to approximately 60% is 10 for 5 Hz stimulation and 11 for 10 Hz stimulation. The same is true of the cell shown in Figure 23 which required approximately 30 stimuli presented in both the 10 and 5 Hz stimulation periods. However, this cell displayed a small adaptation at 2 Hz and displayed a small increase in firing when the rate of stimulation jumped from 0.5 Hz to 2 Hz. The magnitude of the responses increased dramatically to 5 and 10 Hz stimulation and the adaptation asymptote for the 5 Hz stimulation was still much
higher than the baseline firing rate at 0.5 Hz. The cell shown in Figure 24 showed a very rapid adaptation to 10 Hz stimulation but was characterized by variable responsivity during adaptation at both 5 and 10 Hz.

The double exponential equation fit to the adaptation data is shown in equation 3

\[ Y = B + A \exp \left( -1\left( \frac{x}{\tau} \right) \right) \]

Where: 
- \( B \) = base firing rate (asymptote)
- \( A \) = Initial amplitude above \( B \)
- \( \tau \) = time constant of adaptation
- \( x \) = time in seconds from beginning of adaptation

The time constants for 5 and 10 Hz adaptation are shown in Table 1. Although in some cells it appears that the factor determining the rate of adaptation is the number of stimulus presentations, in others it is dependent more on time. It is difficult to draw conclusions from such a small sample but it is clear that no one process determines the rate of adaptation in geniculate cells.

**Discussion**

Only one of the 5 geniculate cells showed adaptation to 2 Hz stimulation. For the cell which did show some adaptation, there was only an 8% decline in responsivity. It was possible that the geniculate cells would have continued to fire to 2 Hz stimulation, but the number of spikes reaching the synaptic terminal would have decreased due to local adaptation mechanisms. This was not the case in the five geniculate fibers recorded in the visual cortex which did not show any adaptation to 2 Hz stimulation. A cortical cell recorded near these geniculate fibers did show pronounced adaptation to the 2 Hz stimulation ruling out the possibility that the electrode was in a region of the cortex which is resistant to adaptation. It is therefore likely that the adaptation of receptive fields of simple and complex cells described in chapter 2 is due to a process intrinsic to the cortical cells.
Part II: The specificity of adaptation

Chapter 4:
Adaptation of excitatory and inhibitory interactions underlying direction selectivity

The experiments described in Part I suggest the separate adaptation of excitatory and inhibitory connections within the receptive fields of simple and complex cortical cells. Prolonged stimulation at one point in the receptive field produced strong response decrements on the preferred direction side at receptive field positions which would receive excitatory connections from the point of adaptation. Receptive field positions on the nonpreferred direction side displayed weaker response decrements and often showed facilitation of responses suggesting adaptation of inhibitory connections. The spatial offset of the directional asymmetry of the spread of adaptation was 0.2 $\lambda$ which is close to the optimal spatial offset for apparent motion in simple and complex cells (Baker, 1988; Baker, Baydala, & Zeitouni, 1989; Baker & Cynader, 1986; Baker & Cynader, 1988). The specificity of this adaptation of receptive field infrastructure may be related to the mechanisms underlying direction selectivity and motion perception.

Psychophysically, prolonged unidirectional motion stimulation results in a perceptual motion aftereffect wherein a stationary stimulus appears to move in the direction opposite that of the adapting stimulus. A similar effect is observed in the response behavior of motion sensitive neurons in Area 17 of the cat (Hammond et al., 1985; Hammond et al., 1986; Maffei et al., 1986; Maffei et al., 1973; Marlin & Cynader, 1986; Marlin et al., 1987; Marlin et al., 1988; Movshon et al., 1980; Saul & Cynader, 1988; Saul & Cynader, 1989a; Saul & Cynader, 1989b; Saul & Daniels, 1985; von der Heydt et al., 1978). Prolonged unidirectional motion in a visual cortical unit’s preferred direction decreases the units responses to preferred direction motion while nonpreferred direction motion
responses do not decrease to the same degree (Hammond et al., 1985; Hammond et al., 1986; Maffei et al., 1973; Marlin & Cynader, 1986; Marlin et al., 1989; Marlin et al., 1987; Marlin et al., 1988; von der Heydt et al., 1978). Perhaps more interesting are the effects of prolonged nonpreferred direction smooth motion on direction selective neurons in area 17. Following this nonpreferred direction adaptation most neurons exhibit an increase in their direction selectivity as indicated by the ratio of the preferred direction response to the nonpreferred direction response. These changes in direction selectivity were in most cases associated with a decline in responsivity but can occur even when the cell does not fire action potentials during the prolonged stimulation. It is possible that the prolonged nonpreferred direction stimulation causes an adaptation of an inhibitory input to the cell. Depending on the selectivity of this inhibitory input, either an increase or a decrease in direction selectivity could result. If the inhibition is largely a gain-control mechanism which controls the spike threshold or the EPSP magnitude of a cell, then adaptation of this inhibition would increase responses to both the preferred and nonpreferred directions of motion. This would result in relatively small changes in the direction selectivity of the cell. Alternatively, if the inhibition is a mechanism contributing to direction selectivity itself by inhibiting nonpreferred direction responses, then adapting this inhibition would result in a selective increase in nonpreferred responses and we would observe a decrease in the direction selectivity ratio. However, prolonged stimulation of a cell with either preferred or nonpreferred direction motion usually results in a general decrease in firing. Any observed changes in the direction selectivity of the cell would be the result of the adaptation of both the excitatory and the inhibitory inputs to the cell.

One way to address this issue is to test direction selective neurons with two-bar sequence apparent motion stimuli both prior to and following prolonged unidirectional motion. Apparent motion stimuli have been used extensively recently
to examine the mechanisms underlying direction selectivity in cortical neurons (Baker & Cynader, 1986; Baker & Cynader, 1988; Emerson & Gerstein, 1977; Ganz & Felder, 1984; Movshon et al., 1978a; Movshon et al., 1978b). When comparing preferred and nonpreferred direction sequences with single bar flashes it is possible to measure the amount of inhibition and facilitation associated with preferred and nonpreferred direction motion. In many cells the response to the second stimulus in an apparent motion sequence will be much higher than expected if the apparent motion sequence is in the cell's preferred direction. A cell's response to the second stimulus in a nonpreferred direction sequence is often greatly reduced when compared to the responses to a single flash in the same receptive field position (see Figure 25). We can examine the effects of prolonged unidirectional motion on these inhibitory and facilitory interactions.

Given our knowledge of direction selective adaptation and the asymmetrical spread of position adaptation we can make specific predictions about the effects of prolonged unidirectional motion on inhibition and facilitation. Prolonged preferred direction motion has a greater influence over a cell's responses to stimuli moving in the preferred direction than in the nonpreferred direction (Marlin & Cynader, 1986; Marlin et al., 1987; Marlin et al., 1988). Facilitation may be selectively reduced following prolonged motion in the preferred direction. In addition to this selective decrease in facilitation there is probably a more general effect which reduces the cell's responses to all stimuli and may be related to the rate of activity during the adaptation period. Using apparent motion stimuli it was possible to separate the general adaptation effects from those specific for facilitation.

Prolonged stimulation with flashed stimuli to small subregions of a cortical cell's receptive field produces adaptation effects for which the spread of adaptation across the receptive field is asymmetric and related to the cell's direction selectivity (see Chapters 2 and 3). Stimulation at a single receptive field position appears to
send a wave of facilitation across the receptive field in the preferred direction and a wave of inhibition in the cell's nonpreferred direction such that with prolonged stimulation the wave of excitation is reduced and receptive field positions influenced by this wave show response decrements. Prolonged stimulation at a single receptive field position also reduces the strength of the wave of inhibition and receptive field positions influenced by this inhibition show facilitation of responses following adaptation. Although the presence of these inhibitory and excitatory waves following stimulation at a single receptive field position is based on the asymmetrical adaptation aftereffects, other researchers have investigated this more directly and have reached the same conclusion (Ganz & Felder, 1984). Ganz and Felder (1984) demonstrated facilitation and inhibition within a simple cell subregion by presenting sequences of two-bar flashed stimuli in either the preferred or nonpreferred directions with very small spatial displacements (as little as 4' of arc). These waves of inhibition and facilitation would be larger with moving stimuli and the adaptation effects should be greater following prolonged unidirectional motion than with flashed single point stimulation. We expect prolonged nonpreferred direction stimulation to decrease the inhibition associated with nonpreferred direction apparent motion sequences. This decrease in inhibition will result in an increase in nonpreferred direction responses in cells with little or no nonpreferred direction response prior to adaptation. In cells with a substantial nonpreferred response the adaptation of inhibition could be accompanied by a decrease in responses via a general adaptation process related to the firing rate of the cell (see above). As with preferred direction adaptation, the use of apparent motion stimuli should allow us to parcel out the general and the specific adaptation effects.
Methods

Surgical Procedures and Physiologic Recording

The adaptation of apparent motion was investigated in 28 visual cortical cells collected from eight cats. The general methods for recording single unit activity from the striate cortex of acutely prepared anesthetized cats have been described in detail in Chapter 1.

Measuring $D_{opt}$ and $T_{opt}$

The receptive fields of cortical cells were located and mapped as described in Chapters 1 and 2. Following initial assessments of the cell's orientation, direction and velocity selectivity and the completion of a line-weighting function (see Figure 1), the optimal parameters for apparent motion were determined quantitatively.

To examine the facilitation and inhibition associated with preferred and nonpreferred direction motion responses it was necessary to determine the optimal spatial and temporal parameters for apparent motion (AM). To determine the optimal displacement $D_{opt}$ for apparent motion for each neuron's receptive field, responses were obtained using two optimally oriented bar stimuli flashed sequentially. $D_{opt}$ was determined one of two ways. In the first method one stimulus (reference) was presented at a constant position in the center of the receptive field. The other (the displaced) stimulus was randomly presented at each of the 16 receptive field positions used to obtain an initial line-weighting function giving a range of spatial displacements. The second method consisted of a double line interaction (DLI) procedure with a temporal delay between the presentation of the two stimuli. For this method the two bars were presented symmetrically around the center of the receptive field with the spatial displacement varied as in method 1. That is, stimulus 1 was presented at position 1 while stimulus 2 was presented at
position 15, or stimulus 1 at position 2 and stimulus 2 at position 14. By comparing the responses to "preferred direction" apparent motion sequence (pAM) trials with "nonpreferred direction" apparent motion sequence (npAM) trials at each spatial displacement we were able to determine the optimal spatial displacement for strong direction selectivity for sequentially flashed stimuli. Following a 50 ms delay the reference stimulus was presented for 200 ms. The second stimulus was presented upon the termination of the first stimulus, at 250 ms into the 750 ms record time. The responses for nonpreferred direction displacements were subtracted from preferred direction displacements yielding a difference function whose peak was taken as the $D_{opt}$ for the cell. In cells where this type of analysis yielded an ambiguous difference function, $D_{opt}$ was estimated from the spatial wavelength of the cell based on the line-weighting function or double-line interaction trials (Baker & Cynader, 1986). Once $D_{opt}$ was determined the two stimuli were presented with a spatial displacement equal to $D_{opt}$ while a temporal interaction tuning experiment was performed. This consisted of presenting the two stimuli repeatedly while the temporal delay between the two stimuli was randomly varied between 0 ms and 400 ms. The peak of this temporal interaction tuning profile was taken as the optimal temporal displacement ($T_{opt}$). Baker and Cynader (1988) demonstrated space-time separability of direction selectivity in Area 17 and therefore a complete spatial-temporal interaction experiment was not necessary to determine $D_{opt}$ and $T_{opt}$.

**Apparent motion trials and adaptation experiments**

To determine the extent of facilitory and inhibitory interactions present in the direction selective responses of the neuron, a number of additional conditions were added to the pAM and npAM conditions. These included single flashed conditions where a stimulus was presented at only one of the receptive field positions used in
the sequence conditions, a simultaneous flash (SF) condition in which the temporal delay separating the two stimuli was 0 ms, a spontaneous condition where no stimuli were presented and spontaneous activity was assessed, and two smooth motion conditions where the stimuli were swept through the receptive field at the cell's preferred velocity in either the cell's preferred (pSM) or nonpreferred (npSM) direction of motion (see Figure 25). These eight stimulus conditions were presented randomly a total of 48 times each. The amount of facilitation or inhibition in apparent motion sequences was determined by comparing the responses during sequence conditions to the sum of the two single flash conditions (see results).

Following the initial 48 sweeps of the apparent motion experiments, the cell was subjected to prolonged repeated unidirectional smooth motion in either the cell's preferred or nonpreferred direction of motion. One of the two light slit stimuli served as the adapting stimulus and was repeatedly swept through the receptive field for a period of 1 minute. Following this adaptation phase each of the eight stimulus conditions in the apparent motion experiment was presented once. Immediately upon completion of the one sweep of post adaptation test trials, the adaptation phase was repeated. This adaptation and post-adaptation test sequence was repeated 48 times with the adapting stimulus always having the same direction of motion and the order of stimulus presentation in the post-adaptation test always randomized. Post-adaptation testing was completed within 8 s, before the cell recovered from the previous 60 s adaptation period. Although there could be some recovery within the first 8 seconds, the arrangement of post-adaptation stimulus presentations ensured that over the course of the 48 sweeps each condition was tested an average of 8 times in each of the 8 post-adaptation trial blocks. This ruled out any biases resulting from decay of the adaptation effects during the 8 s test period.
The eight pre- and post-adaptation conditions are represented graphically in the center of each panel while the graph at the right side of each panel shows sample data for that stimulus condition. These eight conditions were presented 48 times each prior to adaptation. Each condition was presented once during the post-adaptation test periods. The order within each block of eight trials was randomized. The adaptation and post-adaptation test was repeated 48 times with no recovery period between the last trial of the post-adaptation test and the beginning of the next adaptation period which resulted in a continued topping up of the adaptation.
The effects of prolonged unidirectional motion on the responses to smooth and apparent motion as well as to simultaneous two bars flash stimuli are shown for four example cells. Left panels (A, C, E, & G) show the adaptation-induced changes in responsivity following prolonged preferred direction smooth motion while the right panels (B, D, F, & H) show the responsivity changes following nonpreferred direction adaptation for the same cells. Solid histogram bars show the total number of spikes occurring in the 48 pre-adaptation trials for each condition while the hatched bars show the post-adaptation responses. Cells A1 and C1 are complex cells (panels A-D) and Cells ap6 and am1 are simple cells (panels E-H). Preferred direction adaptation reduced the responses of the preferred direction responses more than the nonpreferred direction adaptation. The adaptation effects were generally present in all stimulus conditions but were strongest in those conditions which were most like the adapting stimulus.
Results

adaptation-induced changes in responsivity: example cells

Prolonged preferred direction motion reduced neuronal responsivity, while prolonged stimulation in the nonpreferred direction could either increase or decrease responsivity. The complex cell shown in Figure 26 A and B exhibited a dramatic response decrement following preferred direction adaptation but a modest increase in responses following nonpreferred direction adaptation. The effects of preferred direction adaptation were most apparent in the pSM and pAM conditions and resulted in a decrease in the direction selectivity score (from 0.867 to 0.697) while nonpreferred direction adaptation resulted in a small increase in the direction selectivity of the cell (from 0.891 to 0.934). The complex cell shown in panels C and D displayed typical direction selective adaptation in the smooth motion conditions. Following prolonged preferred direction motion the cell's response to pSM was reduced by 207 spikes or 24% while the npSM response dropped by only 43 spikes or 7%. As a result of these changes the direction selectivity ratio dropped from 1.47 to 1.2 and the directional contrast score (P-N / P+N) from 0.19 to 0.09. The apparent motion conditions displayed responsivity changes similar to the smooth motion conditions with the pAM response showing a greater decline than the npAM response. Both the npAM and the SF responses increased following preferred direction adaptation. Nonpreferred direction adaptation produced a general decline in responsivity which was most visible in the npAM response. The direction selectivity ratio of this cell increased following nonpreferred direction adaptation from 1.7 to 1.97 while the directional contrast score increased from 0.259 to 0.33.

The simple cell shown in Figure 26 E and F exhibited a large amount of inhibition to npSM and a modest amount of inhibition to npAM. Following preferred direction adaptation, all flashed stimulus conditions displayed large
reductions in responsivity (approx. 200 spikes or 33%). The pSM response dropped by 308 spikes or 43% while the npSM responses only dropped by 3 spikes or 13%. Nonpreferred direction adaptation increased the pAM responses and the SF responses by approx 200 spikes but the npAM responses increased by only 133 spikes. The npSM response increased by only 3 spikes while the pSM response decreased. The simple cell shown in panels G and H was only weakly direction selective prior to adaptation and reversed it’s direction selectivity following preferred direction adaptation. Each of the flashed conditions displayed relatively equal responsivity decrements. Nonpreferred direction adaptation decreased the responses to pSM and npSM but actually decreased the inhibition in the npAM and SF conditions.

adaptation-induced changes in responsivity: population data

Preferred direction adaptation

The responses to pAM dropped significantly (T=5.77, p<.05) showing a mean decline of 64.79 spikes over the test period (see Figure 27 B). However, there was no significant relationship between the pre-adaptation direction selectivity and the magnitude of the response decrement for either simple or complex cells (Figure 27 B, D, and F) There was, however, a positive relationship between the initial responsivity of the cell and the degree of adaptation-induced decline in responsivity (see Figure 27 A). Although the responsivity of the cells to npAM was less affected by preferred direction adaptation (see Figure 27 C and D), the response to npAM also showed a significant mean decrease of 40 spikes (T=4.19, p<.05). Cells which displayed greater initial responsivity to npAM showed larger declines in responsivity following preferred direction adaptation. The SF responses also (Fig. 27 E and F) showed a mean adaptation-induced responsivity decrement of ~40 spikes of the pre-adaptation baseline (T=3.9, p<.05). The pSM response displayed the greatest
The post-adaptation responsivity (total number of pre-adaptation spikes) is plotted against the post-adaptation responsivity for the three double bar conditions (left Panels) for preferred direction adaptation. Simple cells are shown as open circles (O) while complex cells are filled circles (●). The right panels show the change in responsivity (post/pre *100%) plotted against the pre-adaptation direction selectivity contrast score (DS_c=(P-N)/(P+N)). Cells which are highly direction selective will have DS_c Scores close to 1.0 while nondirectional cells will have DS_c scores near 0.0. Both simple and complex cells showed decreased activity following prolonged preferred direction motion stimulation although a small number of cells showed increased activity following adaptation. Adaptation effects were greater in the preferred direction apparent motion condition than in the nonpreferred condition.
decline (205 spikes) to preferred direction adaptation (T=4.97, p<.05), while the responsivity to npSM did not demonstrate a significant decline following preferred direction adaptation (T=1.66, p>.05) (not shown).

Nonpreferred direction adaptation

Nonpreferred direction adaptation did not induce the same degree of responsivity decrements as did preferred direction adaptation. Only the npSM and the linear sum of the single flash stimulus conditions (LS) displayed significant decreases in responsivity. The npSM response showed a mean decline in responsivity of 33.75 spikes (T=2.2, p<.05). The pSM response was marked by greater variability due to a very large increase in responsivity in one particular cell. There was also a great amount of variability in the pAM and npAM conditions for which a proportion of the cells examined showed increased responsivity following prolonged stimulation in the nonpreferred direction (see Figure 28). Interestingly, the cells which showed increased responsivity to the pAM were all simple cells while those which displayed large reductions in responsivity were all complex cells. The changes in responsivity following nonpreferred direction adaptation for the two groups were significantly different (T=5.37, p<.05) for the pAM condition but not the npAM nor the SF conditions. Each of the single flash conditions and as such the sum of the single flashes showed a significant decline in responsivity. Interestingly, the mean drop of 85 spikes in the LS condition (T=3.66, p<.05) was even larger than that observed for the npSM condition. This suggests that prolonged stimulation in a cell's nonpreferred direction can adapt the responses to single flashes while simultaneously increasing the responses to pSM or pAM (see discussion).
The post-adaptation responsivity (total number of pre-adaptation spikes) is plotted against the post-adaptation responsivity for the three double bar conditions (left Panels) for nonpreferred direction adaptation. Simple cells are shown as open circles (O) while complex cells are filled circles (●). The right panels show the change in responsivity (post/pre *100%) plotted against the pre-adaptation direction selectivity contrast score ($D_{SC}=(P-N)/(P+N)$). Cells which are highly direction selective will have $D_{SC}$ scores close to 1.0 while nondirectional cells will have $D_{SC}$ scores near 0.0. Complex cells showed decreased activity following prolonged preferred direction motion stimulation while many simple cells showed increased activity following adaptation (see text). Adaptation effects were generally nonspecific with similar adaptation effects present in each of the stimulus conditions.
Changes in direction selectivity

Preferred direction adaptation decreased the preferred direction smooth motion responses more than the nonpreferred direction responses (Figure 29 A). This effect was stronger in simple cells. This proportionally larger decrease in the preferred direction response compared to the nonpreferred direction responses indicates a shift in the direction selectivity of the cells. The apparent motion conditions also demonstrate a similar shift in the direction selectivity as the preferred direction apparent motion sequence decreased proportionally more than the nonpreferred direction apparent motion sequence (see panel B).

Nonpreferred direction adaptation produced different effects in the smooth and apparent motion conditions and different effects in simple and complex cells. Simple cells showed large reductions in the nonpreferred direction smooth motion responses but little change in the preferred direction smooth motion responses. Interestingly, both the apparent motion conditions for simple cells showed increased responsivity. Complex cells showed equal adaptation for the preferred and nonpreferred direction smooth motion following nonpreferred direction adaptation but with a slightly larger reduction of the preferred direction apparent motion response than the nonpreferred direction apparent motion response (panel D). This paradoxical increase in nonpreferred direction responses following nonpreferred direction adaptation suggests the adaptation of an inhibitory element controlling the responsivity of the cell (see below).

Changes in nonlinear direction selective mechanisms

To determine the effects of adaptation on the facilitatory and inhibitory interactions of the apparent motion sequences, for each cell the preferred and nonpreferred direction sequence responses and the responses to the simultaneous two
Figure 29 caption

The changes in preferred direction responsivity are plotted against the changes in nonpreferred direction responsivity for complex (●) and simple (○) cells following adaptation in the preferred or nonpreferred directions. The post adaptation response to the stimuli were divided by the pre adaptation responses and multiplied by 100%. Panels A and B show the preferred verses nonpreferred direction responses following preferred direction adaptation. Panels C and D show the changes in smooth and apparent motion responses following nonpreferred direction adaptation. The 45° line represents where each point would be if there was equal adaptation in the preferred and nonpreferred direction responses. Points above this line indicate greater adaptation of preferred direction responses.
bar flash condition were compared to the linear sum of the two single flash conditions. The ratio (\( \times 100\% \)) of the two bar flash conditions (pAM, npAM or SF) to the linear sum gave a measure of the degree of facilitation and inhibition present in each condition with 100% representing simple linear summation of the two single flashed responses (LS). Scores greater than 100% represent deviations from linear summation (DLS) which are facilitatory and scores less than 100% represent inhibition. The adaptation-induced changes in the DLS of the two bar interaction conditions for complex and simple cells are shown in Figure 30.

**Preferred direction adaptation**

Although there were great changes in the responsivity of the complex cells following preferred direction adaptation (see Figure 28 A), there was no significant decline in the mean DLS score for any of the three two-bar flash conditions for complex cells. However, two cells which were initially facilitated by pAM displayed a large change in their DLS scores (Figure 31, panel A). Furthermore, there was a significant correlation between the initial DLS score and the change in DLS scores following preferred direction adaptation (\( R^2 = .356; F = 6.63, p < .05 \)). The mean DLS score for the npAM condition was also unchanged by preferred direction adaptation. Although there was no change in the mean DLS score for the SF condition (see panel E) there was a significant relationship between the change in DLS score and the amount of inhibition indicated by the pre-adaptation DLS score (\( R^2 = .463; F = 7.32 \)).

The effects of preferred direction adaptation on simple cells were more interesting than those of complex cells. Those simple cells displaying facilitation to the pAM showed an adaptation-induced drop in their DLS scores (Figure 30 A and 31 B). More interesting are the changes in the DLS scores to npAM . Following preferred direction adaptation many simple cells (9/15) which were initially inhibited
The pre-adaptation deviation from linear summation (DLS) score is plotted against the post-adaptation DLS score for each of the double-line interaction conditions for complex (●) and simple cells (○). The prolonged stimulation was in the cell's preferred direction of stimulus motion. For each cell, the responsivity to the interaction condition was expressed as a percent of the expected response based on the linear sum of the two single flash responses. The deviation from linear summation indicated the degree of facilitation or inhibition resulting from the sequential or the simultaneous presentation of the two bar stimuli. The solid diagonal line indicates where each point would lie if the DLS score did not change following adaptation. Points falling below the 45° line represent cells for which the DLS score decreased while points above the line represent increased DLS scores. Of the three double bar flash conditions, the preferred direction apparent motion sequence was greatest affected by the prolonged preferred direction smooth motion. The DLS scores of the preferred direction sequence showed a decrease following adaptation (Panel A). The nonpreferred direction sequence DLS scores increased for simple cells but did not significantly change for complex cells (Panel B).
The preferred-direction-adaptation-induced change in DLS scores (Post DLS - Pre DLS) are plotted against the pre-adaptation DLS scores for each of the three double flash stimulus conditions. The change in DLS scores for complex cells (●) are shown in the left panels while those of simple cells (○) are shown on the right. The magnitude of the change in DLS scores was correlated with the pre-adaptation DLS scores for each condition and for simple and complex cells. The resulting regression lines are presented in each panel. The greater the inhibition present (DLS scores less than 100% on the abscissa), the greater the increase in DLS scores following preferred direction adaptation. The greater the facilitation (DLS > 100%), the greater the decrease in DLS scores following adaptation.
Complex cells

A

Preferred direction sequence

Complex cells

B

Preferred direction sequence

Simple cells

C

Nonpreferred direction sequence

Simple cells

D

Nonpreferred direction sequence

E

Adaptation-induced change in the % deviation from linear summation

Simultaneous 2-bar flash

F

Simultaneous 2-bar flash

Preadaptation Deviation from Linear Summation
by npAM became less inhibited and their DLS scores decreased. In two cells the inhibition was replaced by facilitation. The regression equation fit to the change in DLS scores (Figure 31 D) shows a significant relationship between the initial DLS score and the magnitude of the change in DLS ($R^2=.590$; $F=15.83$, $p<.05$). Cells with greater inhibition associated with npAM displayed larger changes in DLS scores. A similar trend can be seen in 31 F which shows a significant correlation between the initial DLS score and the change in the DLS score for the SF condition ($R^2=.338$; $F=5.62$, $p<.05$).

The changes in the DLS scores represent a change in the responsivity in the apparent motion condition which are more specific than the general changes in responsivity of the cell because the DLS score is a ratio of the responses to the sequence divided by the sum of the single flashes. If we compare the changes in responsivity of the two apparent motion conditions and the single flashed conditions for simple cells we see that, generally, the responses to the pAM and the single flash conditions have decreased equally. However, the responses to the npAM have decreased less than the responses to the single flashes, thereby reducing the difference between the sum of the single flashes and the npAM. Therefore the npAM is less inhibitory following adaptation in the preferred direction. These effects are paralleled by differences in the amount of adaptation observed in the two smooth motion conditions. Preferred direction adaptation decreased the responses to pSM proportionally more than the responses to npSM and in many cases the npSM responses were higher following preferred direction adaptation. This resulted in decreased direction selectivity following preferred direction adaptation for simple cells. However, in complex cells both the pAM and npAM and the two single flash conditions decreased by the same amount and many fewer cells displayed selective changes in the pSM responses.
Figure 32 caption.

The change in DLS scores is plotted against the pre-adaptation direction selectivity contrast score for each of the three double flash conditions for both simple and complex cells. The contrast score was derived using the equation $P-N/P+N$ where $P$ is the pre-adaptation preferred direction smooth motion response and $N$ in the pre-adaptation nonpreferred direction smooth motion response. The change in DLS scores were not significantly correlated with the pre-adaptation direction selectivity contrast score for either apparent motion sequence condition (panels A-D) or the simultaneous condition (panels E & F).
Preadaptation direction selectivity score (P-N)/(P+N)
We might expect there to be a relationship between the initial direction selectivity of the cell and the adaptation-induced change in DLS scores as highly direction selective cells would evoke more selective adaptation while non-directional cells would evoke a more general adaptation. However, there was no apparent relationship between the direction selectivity score and the change in DLS for either simple or complex cells for any of the three two-bar flash conditions (see Figure 32.)

Nonpreferred direction adaptation

There is a striking difference between the effects of preferred (Figures 30-32) and nonpreferred direction (Figures 33-35) adaptation on the DLS scores. The nonpreferred direction adaptation increased the deviation from linear summation in the majority of simple and complex cells tested. Although, the majority (57%) of complex cells showed an increased DLS scores for the pAM condition following nonpreferred direction adaptation (see Figure 33), the mean DLS score did not change (T=1.76, p>.05). A similar increase in the mean DLS score was observed for the npAM for complex cells (panel B). The mean DLS score for the SF condition, however, was significantly (T=3.95, p<.05) higher following nonpreferred direction adaptation (see Fig 33 C and 34 E). The changes in DLS scores for complex cells were not significantly correlated with the pre-adaptation DLS for the cells in any of the two bar flash conditions.

Simple cells displayed even larger increases in DLS scores than did complex cells (see Figures 33 and 34). Clearly adaptation in the nonpreferred direction increased the DLS in the majority of cells for the pAM, npAM and SF conditions. The pAM condition showed a significant mean increase in the DLS (μ=22.01; T=4.32; p<.05). Both the npAM and SF conditions showed a significant mean increase in DLS scores; (μ=16.99; T=2.62; p<.05) and (μ=14.25; T=2.65; p<.05),
The pre-adaptation deviation from linear summation (DLS) is plotted against the DLS score for each of the double-line interaction conditions following prolonged nonpreferred direction smooth motion stimulation for complex (●) and simple cells (○). For each cell the responsivity to the interaction condition was expresses as a percent of the expected response based on the linear sum of the two single flash responses. The deviation from linear summation indicated the degree of facilitation or inhibition resulting from the sequential or the simultaneous presentation of the two bar stimuli. The solid diagonal line indicates where each point would lie if the DLS score did not change following adaptation. Points falling below the 45° line represent cells for which the DLS score decreased while points above the line represent increased DLS scores. Each of the three double bar flash conditions displayed a general increase in the DLS scores for both complex and simple cells. The changes in DLS scores were greater in simple cells.
A

Preferred direction sequence

B

Nonpreferred direction sequence

C

Simultaneous 2-bar flash

Preadaptation Percent Deviation from Linear Summation

Postadaptation Percent Deviation from Linear Summation
The nonpreferred-direction-adaptation-induced change in DLS scores (Post DLS - Pre DLS) are plotted against the pre-adaptation DLS scores for each of the three double flash stimulus conditions. The change in DLS scores for complex cells (●) are shown in the left panels while those of simple cells (○) are shown on the right. The magnitude of the change in DLS scores was correlated with the pre-adaptation DLS scores for each condition and for simple cells but not for complex cells. The regression lines for each data set are presented in each panel. This effect is most clear in the nonpreferred direction apparent motion sequence condition in panel D.
Adaptation-induced Change in Percent Deviation from Linear Summation

A

Complex Cells

100 Preferred direction sequence

B

Simple Cells

100 Preferred direction sequence

C

100 Nonpreferred direction sequence

D

100 Nonpreferred direction sequence

E

Adaptation Percent Deviation from Linear Summation

F

Simultaneous 2-bar flash

Simultaneous 2-bar flash

Preadaptation Percent Deviation from Linear Summation

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Figure 35 caption

The nonpreferred-direction-adaptation-induced change in DLS scores is plotted against the pre-adaptation direction selectivity contrast score for each of the three double flash conditions for both simple and complex cells. The contrast score was derived using the equation P-N/P+N where P is the pre-adaptation preferred direction smooth motion response and N in the pre-adaptation nonpreferred direction smooth motion response. The change in DLS scores were not significantly correlated with the pre-adaptation direction selectivity contrast score for either apparent motion sequence condition (panels A-D) or the simultaneous condition (panels E & F).
Preadaptation direction selectivity score (P-N)/(P+N)
respectively. The increase in DLS was not correlated with the pre-adaptation DLS and so was not related to the amount of facilitation or inhibition in the cell's responses to the stimulus condition. The change in DLS following nonpreferred direction adaptation was not significantly correlated with the pre-adaptation direction selectivity ratio in either simple or complex cells (see Figure 35).

Figure 36 directly compares the adaptation-induced changes in DLS scores for the two-bar flash conditions. Following preferred direction adaptation, the changes in DLS scores of the pAM and npAM were similar for complex cells as there was little change in either condition. The complex cells which did display decreased DLS scores following adaptation in the preferred direction showed smaller changes in the DLS scores of the npAM and SF conditions. While ADLS scores for the preferred and nonpreferred sequences were significantly correlated (slope=.526; $r^2=.496$; $F=11.8$; $p<.05$) the ΔDLS scores for the SF condition were not significantly correlated with those of the pAM (slope=.12; $r^2=.064$; $F=.823$; $p>.05$). Simple cells showed a greater variability of ΔDLS for the npAM and SF conditions following preferred direction adaptation. While the majority of cells showed a decrease in the DLS score for pAM, few simple cells displayed a decrease in the DLS score for the npAM. The npAM ADLS was not significantly correlated with the ΔDLS of the pAM (slope=.28; $r^2=.065$; $F=.765$; $p>.05$). Even though there was a great amount of variability in the ΔDLS for the SF condition for simple cells there was a significant correlation between the ΔDLS for the pAM and the SF conditions (slope=.975; $r^2=.326$; $F=5.33$; $p<.05$).

Following nonpreferred direction adaptation the DLS scores for the pAM increased in both complex and simple cells. There were similar increases in the DLS scores of the npAM and SF conditions. In complex cells the npAM ΔDLS was significantly correlated with the ΔDLS for the pAM (slope=1.05; $r^2=.471$; $F=9.8$;
Figure 36 caption

The adaptation-induced changes in DLS scores for the preferred direction sequence are plotted against the changes in DLS scores for the nonpreferred direction sequence (●) and the simultaneous double flash conditions (○). Panels A and B show the effects of preferred direction adaptation on the DLS scores of complex and simple cells respectively. Panels C and D show the effects of nonpreferred direction adaptation on the DLS scores. Panel A shows greater changes in DLS scores for the preferred direction sequence for complex cells than for either the nonpreferred sequence or the simultaneous condition. Panel B shows a general decrease in the DLS scores of simple cells for the preferred direction sequence and changes in the DLS scores for the nonpreferred direction sequence which are uncorrelated with those of the preferred direction sequence. Panels C and D show a general increase in the DLS scores of all three conditions. The changes in DLS scores for the preferred direction sequence were significantly correlated with the changes in the nonpreferred direction sequence DLS scores for complex cells (panel C) but not for simple cells (panel D).
Preferred Direction Adaptation

A

Complex cells

B

Simple cells

Nonpreferred Direction Adaptation

C

Complex cells

D

Simple cells

Change in % deviation from linear sum of the Preferred sequence

- Nonpreferred Direction Sequence
- Simultaneous Two-Bar Flash
p<.05) but the ΔDLS for the SF condition was not (slope=.28 ;r^2=.066; F=.84; p>.05). In simple cells the ΔDLS for the pAM was not significantly correlated with either the npAM ΔDLS (slope=.31 ;r^2=.066; F=.707; p>.05) or the SF ΔDLS (slope=-.258 ;r^2=.036; F=.373; p>.05) despite the general increase in DLS scores for all conditions.

Preferred versus nonpreferred direction adaptation

The changes in DLS scores following preferred direction adaptation plotted against those following nonpreferred direction adaptation are shown in Figure 37 for the subpopulation of cells in which both experiments were completed. There was not a significant correlation between the changes in DLS scores for preferred and nonpreferred direction adaptation. The DLS scores for the pAM increased in most cells following nonpreferred adaptation and decreased following preferred adaptation. However, the changes observed following nonpreferred adaptation were much larger. The mean changes in the pAM DLS scores following preferred direction adaptation were significantly different from the those following nonpreferred direction adaptation for both complex (T= 3.01, p<, 05) and simple cells (T= 6.63, p<, 05) (see panel B). The npAM condition also showed an increase in DLS scores following nonpreferred direction adaptation but did not show a mean decrease following preferred direction adaptation (panels C and D). Panel D shows that, although there is a great deal more variation in the changes in DLS scores for the nonpreferred sequence, there is still a significant effect of adaptation direction for both complex (T= 2.28, p<, 05) and simple cells (T= 2.65, p<, 05). The effects observed for the SF condition were similar to those of the preferred direction sequence with preferred direction adaptation decreasing the DLS scores and nonpreferred direction adaptation increasing the DLS scores in the same cells (see
The change in DLS scores following preferred direction adaptation are plotted against the changes in DLS scores following nonpreferred direction adaptation for the complex (■) and simple cells (○) for which both experiments were performed. Left panels show the scatter plot of these data for the preferred, nonpreferred and simultaneous conditions while right panels show the mean adaptation-induced change in the DLS scores following preferred and nonpreferred direction adaptation. Nonpreferred direction adaptation resulted in a general increase in DLS scores in both complex and simple cells. The effects of preferred and nonpreferred direction adaptation on the DLS scores were significantly different for both simple and complex cells for both the pAM and npAM and for complex cells in the SF condition.
panels E and F). There was no significant correlation between the changes in DLS for the SF condition following preferred and nonpreferred direction adaptation. However, the changes in DLS scores in simple cells were more variable and the differences between preferred and nonpreferred direction adaptation were not significant (T= 1.39, p > 0.05). The effects of preferred and nonpreferred direction adaptation were significantly different for complex cells (T= 2.96, p < 0.05).

Discussion

Adaptation to prolonged unidirectional motion similarly affect apparent and smoothly moving stimuli. Generally, preferred direction adaptation decreased the responses to all stimulus conditions but the decrease was strongest in the pSM and pAM conditions. Nonpreferred direction adaptation decreased the responsivity in most complex cells but had different effects in simple cells. Although there was a decrease in the responses of simple cells to npSM, the responses to each of the flashed stimulus conditions increased.

Preferred direction adaptation effects

Although prolonged stimulation in the preferred direction resulted in a general decrease in the responsivity of both simple and complex cells, the magnitude of the adaptation effects were strongest in the pSM and pAM conditions. The most likely explanation for the general effects observed following preferred direction adaptation is that the adaptation effects a general property of the cell which controls excitability. The changes in responsivity were larger for pAM stimulation when the adaptation was in the preferred direction than for npAM or the sum of the two single flashes. The DLS decreased following adaptation in the preferred direction as a result of this differential adaptation of the pAM and the single flashed responses. The changes in
the responsivity to npAM were more closely tied with changes in responsivity to the single flashes suggesting a general adaptation process. The more dramatic changes in the pAM and pSM conditions suggest the adaptation of specific multiplicative interactions such as nonlinear facilitation of preferred direction responses. Furthermore, the changes in the sequence conditions are closely matched with the direction selective adaptation effects observed with smoothly moving stimuli in the present and previous experiments (Marlin & Cynader, 1986; Marlin et al., 1987; Marlin et al., 1988). Preferred direction adaptation reduces the direction selectivity of striate cells by reducing the preferred direction responses proportionally more than the nonpreferred direction responses. If we assume that the excitatory and inhibitory interactions observed in the apparent motion sequences are related to the direction selectivity of the cortical cells, we can then conclude that the changes in the direction selectivity observed following prolonged preferred direction stimulation result from a decrease in the facilitatory interactions between certain receptive field subunits.

*Nonpreferred direction adaptation effects*

Nonpreferred direction adaptation reduced the responses of cortical cells to a lesser degree than preferred direction adaptation. However, despite the weaker adaptation, there were stronger adaptation effects on the facilitatory and inhibitory nonlinearities associated with the apparent motion sequences. Almost all of the cells examined displayed increased facilitation or decreased inhibition following prolonged stimulation in the nonpreferred direction. These changes were largest for cells for which the two bar interaction indicated inhibition. If prolonged stimulation in a cell's nonpreferred direction selectively adapted an inhibitory network, then it is not surprising that the inhibitory nonlinearities would decrease relative to the single flashes. Assuming that the inhibition results from a single flash and is propagated
across the receptive field in the cell's nonpreferred direction, then we would not observe this inhibition when we stimulated the receptive field with a single flash but this inhibition would be clearly visible if a second flash was presented with the appropriate spatial and temporal offset. Using sequentially presented stimuli, Goodwin and Henry (Goodwin et al., 1975) demonstrated a wave of inhibition propagated in the cell's nonpreferred direction that could be initiated by a single flash presented in a cell's receptive field. They suggested that a powerful inhibition is initiated by a stimulus moving in a cell's nonpreferred direction and that the inhibition moves along with, and ahead of, the moving stimulus.

Prolonged stimulation in a cell's nonpreferred direction could result in an adaptation of this inhibitory wave or the inhibitory network responsible for the wave. This would result in an increase the response to nonpreferred direction motion. However, there could also be a general decrease in the responses of the cortical cell due to intrinsic adaptation mechanisms. This would be reflected by a decreased response to flashed stimuli as well as to moving stimuli. The sum of these two independent processes would be observed in the responses to the various flash conditions following nonpreferred direction adaptation.

**Simple versus complex cells**

Both simple and complex cells displayed adaptation of the facilitatory and inhibitory interactions to the apparent motion sequences. Simple cells, however, displayed more inhibition to nonpreferred direction apparent motion sequences and also displayed a greater change in DLS scores following adaptation. The greater effects in simple cells may reflect a more unilateral mechanism for direction selectivity in those cells. It has been suggested that, in the majority of simple cells, the direction selectivity exclusively results from inhibition of nonpreferred direction motion across the receptive field by strong GABAergic interactions within the
receptive field (DeValois et al., 1982; Douglas & Martin, 1991; Ganz, 1984; Tsumoto, Eckart, & Creutzfeldt, 1982). Complex cells are thought to combine both facilitation and inhibition to produce direction selectivity. The present experiments demonstrated that although the changes in overall responsivity were similar for simple and complex cells the changes in DLS scores were greater in simple cells. The adaptation effects observed in complex cells may reflect three separate mechanisms which include: 1) general adaptation effects; 2) adaptation of facilitation; and 3) adaptation of inhibition. It appears that in complex cells the general effect dominates and the result of prolonged stimulation in the cells preferred direction is a decrease in both preferred and nonpreferred direction responses. Simple cells are dominated by inhibitory interactions and therefore the prolonged stimulation in the preferred direction results in an adaptation of preferred direction responses but minimal changes in the nonpreferred direction responses. Nonpreferred direction adaptation, on the other hand, evokes a general adaptation process and decreases inhibitory interactions. In cells where the nonpreferred direction responses are very low, adaptation in the nonpreferred direction decreased the influence of the inhibitory interactions and as a result there was a general increase in responsivity to nonpreferred direction stimuli. Many cells have shown an increase in the preferred direction responses following adaptation in the nonpreferred direction suggesting the existence of a general inhibitory process, regulating the gain of the responses (Martin et al., 1988).
Part III

The mechanisms of adaptation

Parts 1 and 2 of this thesis demonstrate the specificity of adaptation for position and direction of motion. The prolonged stimulation of a subregion of a visual cortical cell's receptive field results in a localized decrease in the responses to subsequent stimulation near that subregion. Furthermore, the adaptation spreads asymmetrically across the receptive field of both simple and complex cells and the spread of adaptation is related to the direction selectivity of the cell. The adaptation of local interactions within the dendritic field of the cells may account for this phenomenon. Alternatively, it is possible that the adaptation observed in these cortical cells reflects the adaptation of cells closer to the retina (i.e. the afferents to the cortical cells). Although the cells in the LGN did not show significant adaptation to 2 Hz stimulation and continued to discharge spikes at a high rate, the spikes entering the nerve terminal at the level of the visual cortex may be shunted by local inhibitory connections. These inhibitory connections could be initiated by local feedback mechanisms to control the gain of the cortical cells to changes in general luminance or contrast levels (Ohzawa et al., 1982; Ohzawa et al., 1985; Sclar et al., 1985) or to reduce the release of excitatory amino acids from the geniculate synapses controlling the excitability of cortical neurons to prevent glutamate excitotoxicity (Benveniste, Jorgensen, Sandberg, Christensen, Hagberg, & Diemer, 1989; Nicholls & Attwell, 1990; Piredda & Gale, 1986; Sanchez & Gonzalez, 1988; Volpe, 1989; Zevelk, Hyndman, & Nicklas, 1989; Zevelk & Nicklas, 1989). Vidyasagar (1990) suggests that the adaptation of cortical neurons results from the activation of a cooperative network within the cortex to control the excitability of the cortical cells. He argues that the control of the gain of the response of the cortical cells rests in local excitatory interactions within this network and that adaptation results in a local decrease in the excitation from this network.
However, it is equally likely that the control occurs via local inhibitory interactions (Wilson, 1975). The local inhibitory network would be strengthened with prolonged stimulation such that the resulting adaptation would be selective for the stimulus parameters presented during prolonged stimulation (Wilson, 1975).

There are a large number of candidates for the agents controlling Wilson's (1975) proposed inhibitory feedback network underlying adaptation. These inhibitory agents include classical neurotransmitters and peptides as well as voltage-dependent ion channels (see general discussion) (Albrecht, Pearce, & Murphy, 1986; Bianchi, Tanganelli, Marzola, & Beani, 1982; Blaker, 1985; Brailowsky & Knight, 1984; Collins et al., 1984; Connors, Malenka, & Silva, 1988; Dichter, 1980; Dykes, Landry, Metherate, & Hicks, 1984; Faingold, Gehlback, & Caspary, 1989; Fillenz & Bloomfield, 1986; Gee, Lawrence, & Yamamura, 1986; Guilarte, 1989; Herrling, 1984; Katayama, Miyazaki, Tsubokawa, & Moriyasu, 1981; Kayama, 1985; Kontro & Oja, 1987; Lust, Assaf, Ricci, Ratcheson, & Sternau, 1988; Luu, Morrow, Paul, & Schwartz, 1987; Maksay & Ticku, 1984; Mamchur, 1987; McBride & Frederickson, 1980; McCormick, 1989; Muller & Singer, 1989; Nishikawa & Scatton, 1985; Rayevsky, Kovalev, Kharlamov, & et, 1984; Sagratella & Massotti, 1982; Sato & Tsumoto, 1984; Scatton & Bartholini, 1980; Schousboe, Frandsen, & Drejer, 1989; Snodgrass, White, Biales, & Dichter, 1980; Storm, 1990; Suzdak & Gianutsos, 1985b; Tsumoto et al., 1982; Verhage, Besselsen, Lopes, & Ghijsen, 1989).

The classical inhibitory neurotransmitter GABA has been proposed as the mechanism underlying the adaptation of cortical neurons and will be examined in detail in Chapter 5. The activation of the hyperpolarizing K+ channels some receptors including the GABA-B receptor in some cortical cells may underlie the adaptation to prolonged stimulation. The sAHP has temporal properties similar to adaptation. Both adaptation of responsivity and the sAHP decay slowly with time constants of 5-15 seconds (Schwindt et al., 1988a). The sAHP results from the opening of a subclass of voltage-insensitive calcium-dependent potassium channels. There
are three subclasses of CA(2+) dependent K+ channel currents which are of interest: a fast-decaying afterhyperpolarization (fAHP); a subsequent medium-duration afterhyperpolarization (mAHP) which follows a single spike; and a slower afterhyperpolarization (sAHP) activated by sustained repetitive firing (Schwindt et al., 1988b). The K(+) conductance underlying the mAHP controls the instantaneous firing rate during prolonged stimulation, but not the time course of slow adaptation (Schwindt et al., 1988b). The sAHP has two components which are sensitive to membrane potential and raised extracellular K(+) concentrations (Schwindt et al., 1988a). The time constants of these two components are strikingly different. The early sAHP decayed within several hundred milliseconds while the late sAHP took several seconds (Schwindt et al., 1988a). Thus, there is a possibility that the early sAHP may control the initial fast adaptation observed in many visual cortical cells which also appear to have two separate exponential rates of adaptation (for examples see Figure 40).
Chapter 5

The role of GABAergic inhibition in the adaptation of visual cortical neurons.

The neurotransmitter γ-amino-butyric acid (GABA) inhibits the activity of neurons in a large variety of species and brain regions (Sivitoti & Nistri, 1991). There are two known distinct GABA receptors which give rise to the inhibitory effects of GABA. The GABA-A receptor is widespread throughout the brain and is reversibly blocked by bicuculline (Sivitoti & Nistri, 1991). The GABA (B) receptor has only recently been discovered and it appears that it is not as widely distributed. The GABA-B receptors can be reversibly blocked by phaclofen (Sivitoti & Nistri, 1991).

GABA-A inhibition acts via an increase in chloride (Cl⁻) conductance (gCl), which decreases the input resistance of the cell, and drives the membrane potential more negative toward the chloride equilibrium potential of -75 mV (Dichter, 1980; Duffy, Burchfiel, Mower, 1985; Gee et al., 1986; Luu et al., 1987; Nowak, Young, & MacDonald, 1982; Olsen & Snowman, 1982; Olsen & Snowman, 1983; Scholfield, 1982; Supavilai, Mannonen, Collins, & Karobath, 1982). The GABA-A receptors are located close to or as part of the Cl⁻ channel.

Iontophoresis of bicuculline in the form of bicuculline methiodide (BMI) has been shown to elevate the firing rate and burst firing in visual cortical cells. Bicuculline binds to and blocks endogenous GABA binding to the GABA receptor-gated Cl⁻ channel. However, bicuculline does not block the shift in the contrast response function (CRF) of cortical cells that occurs following prolonged stimulation (DeBruyn & Bonds, 1986; Vidyasagar, 1990). Although blocking the GABA-A receptors did not alter the shift in the CRF, this study does not rule out a role for GABAergic inhibition in adaptation as it is possible that the time course of adaptation was affected. Neither Vidyasagar (1990) nor DeBruyn (1986) examined the time course of
the adaptation itself. In cortical neurons the adaptation to prolonged stimulation can be approximated by a double exponential equation (see Chapter 4) with a very fast time constant (ms to a few seconds) and a much slower time constant (tens of seconds). The bicuculline may eliminate only one of these components while the other process may effectively reduce the cells responses to stimuli at lower contrasts. It is plausible to suppose that, if the GABA-A receptor is involved in the adaptation of cortical neurons, bicuculline would block the fast component since the GABA-A effects are rapid. The mechanism underlying the slower component may be the activation of a K+ channel mediated sAHP by the GABA-B receptor. Connors (1988) showed that baclofen, a selective GABA-B receptor agonist, causes a slow hyperpolarization of the resting potential and depressed the size of the EPSPs. Furthermore, baclofen increased the depolarizing current required to produce repetitive firing. Conners (1988) concluded that the GABA-B-induced long duration IPSP increases the threshold for spiking activity and decreases the firing rate to repeated stimulation, while leaving the neuron's responses to strong, transient stimuli unimpaired. There is also evidence suggesting that GABA-B receptors are located presynaptically on glutaminergic terminals and that they modulate the release of endogenous glutamate (Mitchell, 1980; Nielsen, Aarslew, Diemer, Krogsgaard, & Schousboe, 1989; Potashner, 1980; Rossignol, Claperon, & Durussel, 1987; Scholfield, 1983).

GABA-B inhibition is evoked after repeated stimulation (Collins, Anson, & Kelly, 1982; Dutar & Nicoll, 1988a; Dutar & Nicoll, 1988b; Howe, Sutor, & Ziegglansberger, 1987; Ogawa & Kato, 1982; Storm, 1990) and therefore is a likely candidate for the mechanism of adaptation proposed by Wilson's (1975) feedback inhibition model. In his model, repeated co-activation of the pre-synaptic and post-synaptic processes will enhance the strength of that synapse. According to this model, the excitatory synapses become less effective due to the increasing inhibition uncoupling the pre-synaptic
excitatory input from the post-synaptic response. That is, with increased inhibition the probability of the postsynaptic cell firing a spike in response to the afferent fiber releasing an excitatory transmitter becomes less and less with repeated stimulation until the two responses are completely uncorrelated. With prolonged stimulation the inhibitory synapses become stronger while the excitatory synapses become weaker. Wilson suggests that inhibitory inputs have a slightly larger spread across the cortex than the corresponding excitatory inputs such that adaptation at a single spatial frequency would induce potentiation of the inhibitory inputs onto that channel as well as neighboring spatial frequency channels.

If GABA mediated inhibition is involved in the adaptation of cortical neurons then either bicuculline methiodide (BMI), Phaclofen, or simultaneous application of both these antagonists might reduce or eliminate the adaptation effects. If, however, GABA simply alters the signal to noise ratio or the baseline firing rate in these cells, the cells may actually adapt faster if the response rates are increased. The same manipulation will also allow us to see if removing GABA inhibition alters the direction selectivity of the cells, and if so, if the cells demonstrate nonspecific adaptation in the presence of GABA antagonists.

Methods

The methods for recording single unit activity from the striate cortex of acutely prepared anesthetized cats have been described in detail in the general methods. Several alterations in methodology were made to facilitate the use of three barreled glass micropipette recording electrodes.

In all experiments a thin carbon fiber (7μ) was inserted into one of the three glass barrels (Armstrong-James & Millar, 1979). The pipette was then pulled to a fine tip with the glass of the recording barrel forming a tight seal around the carbon fiber. The barrel containing the carbon fiber was filled with sodium chloride (0.9%). The other two barrels were filled with either 0.1 M (pH 3.5) BMI (Sigma Chemical Co.),
1.5 mM (pH 3.0) Phaclofen (RBI), or saline. In addition, further data was collected using the agonists 1.0 M (pH 8.0) GABA, 0.1 M (pH 3.5) baclofen (RBI) and 11.8 M (pH 8.0) L-sodium glutamate (Sigma). The impedance of the recording electrode was between 10 and 30 mΩ while the other barrels had typical resistances of between 20 and 80 mΩ. The two drug barrels were filled and the carbon fiber was etched back to within 10-20 μ from the glass tip using a solution of sulphuric acid containing chromate ions (Armstrong-James & Millar, 1979). Attempts were made to use 5 barrelled electrodes to accommodate all drugs and to allow current balancing but adequate isolation of single units under these conditions was not possible. Current controls and balancing were occasionally performed with the 3-barrelled pipette and in those cells where these current controls were made, the currents used did not change the response of the cells. The electrode was placed into the microdrive and silver chloride wires with gold plated leads were inserted into each barrel. The lead from the carbon fiber was attached to the preamplifier while the leads from the other two barrels were connected to the Neurophore iontophoresis unit (Medical Systems Corp.). A small hole was made in the dura of the anesthetized and paralyzed cat. The electrode was lowered into the hole in the dura with the aid of a binocular dissecting microscope. A small retaining current (± 7-20 nA) was applied to each drug barrel to prevent leakage. The electrode was advanced in 25μ steps until a cell could be isolated. Qualitative and quantitative studies were made to determine the optimal stimulus for the cell and to classify the cell as simple or complex. A typical adaptation experiment was performed in the absence of any drug to establish a baseline adaptation rate for the cell. In a number of cells preliminary experiments were made to determine the effective current of BMI and phaclofen which would result in a change in the spontaneous and stimulus evoked firing rate of the cell. BMI was effective at currents of 25 to 60 nA while phaclofen was often ineffective.
in raising the baseline firing rate at all current levels but was sometimes effective at currents between 100 and 200 nA. Phaclofen could be ineffective on one cell but alter the firing rate of a cell 100μ further along within the same penetration.

**Experimental procedures**

Cells were initially tested for orientation, direction, spatial frequency, and velocity tuning to determine the best stimulus for the adaptation experiments. Then the cells were subjected to a series of conditions (see Figure 38). In phase 1 the normal responses of the cell and the adaptation of responsivity to prolonged unidirectional motion were tested with the retaining currents set to minimize leakage of the pipette solutions. The first event in the sequence was an assessment of the responses to the preferred and nonpreferred directions of motion of the optimal stimulus as well as recording the spontaneous activity. Each of these three conditions was tested five times with the order within any one block of three trials randomized ("test"). The cell was then presented with prolonged unidirectional motion in the cell's preferred direction. Some experiments also included nonpreferred direction adaptation trials. Immediately following the period of adaptation the cell's responses to the preferred and nonpreferred direction of motion and spontaneous activity were assessed once each. The order of presentation in this block of trials was randomized. A 30 sec period of recovery separated the end of the post-adaptation trials and the beginning of another adaptation cycle. The adaptation and test cycle was repeated five times. The drug was then applied iontophotically for 30 to 180 seconds prior to the beginning of, and for the duration of the pre-adaptation, adaptation, and test cycle (phase 2). In many cells an additional test was made immediately following cessation of the drug application. The duration of the drug application varied from 10 to 25 minutes depending on the number of adaptation cycles. Recovery tests were made at 5, 10
The sequence of adaptation and test trials employed during experiments involving iontophoretic application of GABA antagonists while recording the responses of single cells in the cat visual cortex. A "test" consisted of a presentation of preferred and nonpreferred direction smooth motion and a period during which spontaneous spikes were assessed (Panel A). The adaptation consisted of 30, 45 or 60 seconds of unidirectional smooth motion (usually in the cell's preferred direction). The adaptation was immediately followed by a single presentation of each of the test conditions (randomized). The adaptation and post-adaptation test cycle was repeated 5 or 10 times. Following an initial test of the effects of prolonged unidirectional motion, the drug application began and preceded further testing by at least 60 seconds. The adaptation and post-adaptation experiments were performed in the presence of the GABA antagonists and at 5 or 10 and 15 minutes following cessation of the drug application.
5 repetitions of each stimulus condition (randomly presented)

Preferred

Nonpreferred

Spontaneous

60 seconds of unidirectional motion

1 repetition of each stimulus condition (randomly presented)

Repeat 5 times
and 15 minutes following the cessation of the drug application. This entire sequence was repeated in most cells and in many cells with different ejection currents.

Results

BMI increased the responsivity of all cortical cells by as much as 400%. The bursting was also increased by BMI. In many cells the BMI resulted in poorer single cell isolation due to recruitment of previously silent cells in the area surrounding the electrode and the trial was discontinued. Only cells which could be isolated throughout the entire sequence were included in the study. In one experiment the BMI was applied for 2 hours while the effects on spontaneous activity were assessed. The BMI initially increased the activity of the cell while after prolonged application the BMI inhibited both spontaneous and evoked activity in the cell. We therefore allowed at least 30 min between experiments involving repeated application of BMI. Iontophoretic application of GABA reduced the responses of the cell dramatically. In those cells where there were still some responses during GABA, the adaptation occurred as normal. Glutamate increased the responses in a manner similar to bicuculline. However this data was collected in only a small number of cells and the results are not presented here.

Neither BMI nor phaclofen blocked the adaptation of responses of visual cortical cells to prolonged stimulation. Figures 39, 40 show the data obtained from 2 typical cells. 30 nA of BMI increased the normal responses but did not block the adaptation to prolonged stimulation in the cell shown in Figure 39. The cell was highly direction selective with the nonpreferred direction responses only slightly above the level of spontaneous activity. The first DS test was in the absence of BMI in phase 2 (see panel B) and the responses are close to those seen in panel A (before adaptation). During 30 nA BMI application (which was initiated 30 sec before
The effects of 30 nA BMI on the responsivity and adaptation of complex cell PH2-C4. The left panel shows the normal adaptation effects on the preferred (■), nonpreferred (⊘) and spontaneous (○) conditions. Direction selectivity tests were performed immediately before and immediately after the adaptation period. In addition there were additional tests of direction selectivity following the cessation of the BMI (center and right panels). The period of BMI application is indicated at the top of each panel.
Pre-bicuculline adaptation test

30 nA Bicuculline adaptation test

Post-bicuculline adaptation test

Test conditions
- preferred direction responses
- nonpreferred direction responses
- spontaneous responses
The effects of 30 nA BMI on the responsivity and adaptation of complex cell PH2-C2. The left panel shows the normal adaptation effects on the preferred (■), nonpreferred (○) and spontaneous (□) conditions. Direction selectivity tests were performed immediately before and immediately after the adaptation period. In addition there were additional tests of direction selectivity following the cessation of the BMI (center and right panels). The period of BMI application is indicated at the top of each panel.
Pre-bicuculline adaptation test

Post-bicuculline adaptation test

Number of Spikes in 10 Repetitions

Time in Seconds

0 50 100 150 200

5 min post adaptation
10 min post bicuculline
15 min post bicuculline

Preferred direction responses
Non-preferred direction responses
Spontaneous responses
testing) the responses to all stimulus conditions were approximately double. The nonpreferred direction response increased to a level well above the spontaneous discharge rate. However, the increased activity under BMI did not prevent adaptation to prolonged stimulation.

The spontaneous activity in the cell shown in Figure 40 was extremely low and the direction selectivity ratio of the cell before adaptation was 1.53:1. Prolonged stimulation in the cell's preferred direction rapidly reduced the firing rate to preferred direction stimulation. The application of 30 nA of BMI had differential effects on the preferred and nonpreferred direction responses. The preferred direction response increased from 177 to 385 spikes in 10 trials (210%) while the nonpreferred direction responses increased from 98 to 323 spikes (330%). The BMI also increased the spontaneous activity by 233% from 6 to 14 spikes. The adaptation was as rapid with BMI (panel B) as without (panel A). The direction selectivity ratio under BMI decreased from 1.19 to 1.05 following prolonged preferred direction stimulation. It appeared that the adaptation reduced the preferred and nonpreferred responses to approximately the same asymptotic level. However, this asymptote was much higher with BMI than without. The responsivity was still elevated 5 minutes after the BMI was turned off but was back to the pre-BMI levels after 10 minutes (panel C). Furthermore, the adaptation observed during this period was similar to that observed prior to BMI. The effects of BMI on the cells shown in Figure 39-40 were observed in each of the 14 cells examined with BMI.

To establish if the changes in the rate of adaptation observed during BMI application in some of the cells was a general effect the adaptation profile in each cell was fit with a double exponential curve (see Figure 41). The pre-bicuculline constants (K0-K4) were plotted against the constants obtained for the curve fits of the adaptation during BMI. The mean baseline firing rate increased by 189.67 spikes during BMI (T=10.73, p<.05). The magnitudes of the two exponentials (the firing
rate above the baseline) k1 and k3 were significant higher under BMI (T_k1=4.40, p<.05; T_k3=3.727, p<.05) (see Figure 41 C and D). The slow phase time constant did not change under BMI (T=1.05, p>.05) while the fast phase time constant showed a significant mean reduction (T=3.9, p<.05) (see Figure 41, panels E and F). This decrease in the time constant of the fast phase of adaptation indicates that the initial decline in responsivity which occurs within the first 1-7 seconds occurs much faster under bicuculline and may be related to the increase in responsivity.

Phaclofen did not change the initial firing rate in 10 of the 13 cells and did not block the adaptation to prolonged stimulation in any of the cells tested (Figures 42-44.). The cell shown in Figure 42 was one of two tested with the GABA-B agonist baclofen as well as the antagonist phaclofen. Baclofen decreased the evoked activity of the cell and also decreased the variability of the responses (see Figure 42 A and B). Phaclofen blocked the effects of baclofen on the responses of the cell (see panel D). In all tests this cell showed a general decline in responsivity to prolonged stimulation. Both the preferred and nonpreferred direction responses decreased by close to 50% in all panels except during phaclofen alone when the nonpreferred direction response decreased by 76%.

The cell shown in Figure 43 was the only cell to show a substantial increase in firing during phaclofen application but this cell also showed normal adaptation during phaclofen (see panel B). The phaclofen effects on responsivity had diminished 5 minutes after the phaclofen application had ceased. Simultaneous application of phaclofen and BMI increased the baseline firing rate more than phaclofen alone (panel C). Despite blocking both the GABA-A and GABA-B receptors, the adaptation to prolonged stimulation occurred as normal. The cell was still demonstrating elevated responsivity 5 minutes after BMI and phaclofen while the responses were normal following an additional 5 minutes of recovery (panel D). The adaptation during this recovery period was still faster than that observed prior to phaclofen.
The effects of BMI on the double exponential curve fit constants for the adaptation of the 14 cells for which BMI adaptation data was obtained. A typical double exponential equation is shown in panel A with the constants k0-k4 illustrated. In each panel, the preBMI value of the constant is plotted on the abscissa while the values during BMI application are plotted on the ordinate. BMI increased the baseline firing rate (Panel B) and the magnitudes of the exponentials (Panels C and D). BMI decreased the fast phase time constant of adaptation (Panel F) but not the slow phase time constant (Panel E).
$$f(x) = k_0 + k_1 \exp(-x/k_2) + k_3 \exp(-x/k_4)$$
The effects of 25 nA baclofen and 125 nA phaclofen on the responsivity and adaptation of complex cell PH2-C1. The left panel shows the normal adaptation effects on the preferred (■), nonpreferred (◇) and spontaneous (○) conditions. Direction selectivity tests were performed immediately before and immediately after the adaptation period. The period of baclofen and phaclofen application is indicated at the top of each panel.
Figure 43 caption.

The effects of 25 nA BMI and 125 nA phaclofen on the responsivity and adaptation of complex cell PH1-C1. The left panel shows the normal adaptation effects on the preferred (■), nonpreferred (□) and spontaneous (○) conditions. Direction selectivity tests were performed immediately before and immediately after the adaptation period. The period of BMI and phaclofen application is indicated at the top of each panel.
Figure 44 caption

The effects of phaclofen on the double exponential curve fit constants for the adaptation of the 14 cells for which phaclofen adaptation data was obtained. A typical double exponential equation is shown in panel A with the constants k0-k4 illustrated. In each panel, the pre-phaclofen value of the constant is plotted on the abscissa while the values during phaclofen application are plotted on the ordinate. Phaclofen did not increase the baseline firing rate (Panel B) or the magnitudes of the exponentials (Panels C and D). Phaclofen decreased the fast phase time constant of adaptation (Panel F) and also the slow phase time constant to some degree (Panel E).
\[ f(x) = k_0 + k_1 \exp(-x/k_2) + k_3 \exp(-x/k_4) \]

A

B

C

D

E

F

K_0 \text{ during Phaclofen}

K_1 \text{ during Phaclofen}

K_2 \text{ during Phaclofen}

K_3 \text{ during Phaclofen}

K_4 \text{ during Phaclofen}

K_0 \text{ prior to Phaclofen}

K_1 \text{ prior to Phaclofen}

K_2 \text{ prior to Phaclofen}

K_3 \text{ prior to Phaclofen}

K_4 \text{ prior to Phaclofen}
Complete adaptation and recovery data sets were obtained for 14 cells with bicuculline and 13 cells with phaclofen. The adaptation data for the control and drug conditions were fit with double exponential curves to determine the effects of bicuculline and phaclofen on the magnitudes of the responses and the time constants of adaptation. Unlike bicuculline, phaclofen did not increase the firing rates of 10 of the 13 cells examined (see Figure 44 B-D). The time constants of adaptation were decreased in most cells during phaclofen application and the population showed a mean decrease in the slow phase tau (τ) (from 30.29 sec to 19.66 sec) as well as the fast phase tau (τ) (from 2.9 sec to 1.3 sec). However, the change in the slow phase time constant (κ2) was not significant (T=1.18, p>.05) even though τ did decrease in 10 of the 13 cells (see Figure 44 E). The change in the time constant of the fast phase of adaptation (κ4) was significant (T=3.44, p<.05) (see Figure 44 F). Five cells showed a dramatic decrease in κ4 and these cells generally had longer time constants initially.

Discussion

Neither bicuculline nor phaclofen blocked the adaptation of visual cortical cells to prolonged stimulation. Therefore, the feedback inhibition model proposed by Wilson (1975) cannot be considered the mechanism of adaptation in visual cortical cells unless the feedback inhibition is via an alternative inhibitory transmitter. Furthermore, the responsivity of the cells was elevated during BMI application and the cells adapted more rapidly. It is not clear whether this change in the rate of adaptation is a function of the GABA (A) receptor inactivation or of the elevation in responsivity per se. Although most visual cortical cells show adaptation to prolonged stimulation, there is a great deal of variability between cells in the rate of adaptation. This variability is not correlated with the initial responsivity of the cell (Albrecht et al., 1984; Marlin & Cynader, 1986). Furthermore, even cells with extremely
high spontaneous firing rates can show relatively poor adaptation.

One possibility is that variability in the rates of adaptation may be related to the difference between the spontaneous and the evoked responses. For example, if a cell is characterized by low spontaneous activity and high evoked discharge rates then the cell may adapt much faster. However, there is not a strong correlation between the signal to noise ratio of a cell and the rate of adaptation in the cells we have examined. Secondly, although the rate of adaptation increased when bicuculline was applied, the signal to noise ratio did not change in most cells. Bicuculline increased the mean baseline firing rate \((k_0)\) and the magnitudes of the exponentials \((k_1\) and \(k_3\)) by approximately 3 times. The ratio of the magnitude of the exponential to the baseline however did not change suggesting that GABA-A receptor activation controls the firing rate of the cells through a process of shunting inhibition which simply divides incoming EPSPs by a constant amount (Blomfield, 1974).

The GABA-B receptor inactivation by phaclofen did not change the adaptation of cortical cells in the direction that was predicted from its known effect on the sAHP via slowly inactivating K\(^+\) channels. Baclofen has been shown to depress evoked EPSPs in cortical cells, thus increasing the stimulation intensity required to produce a synaptically evoked action potential (Collins et al., 1982; Howe et al., 1987; Ogawa & Kato, 1982; Storm, 1990). Baclofen can also depress the postsynaptic response without affecting the duration of the afterhyperpolarization in the terminal. The only clear effect of phaclofen observed here was an increase in the rate of adaptation. Adaptation occurred faster when phaclofen was applied but the asymptote was the same with or without phaclofen. The effect of phaclofen on the rate of adaptation suggests that there were subtle changes in the membrane potential or input resistance which were not evident in the spontaneous or evoked firing rates. The effects were
not as clear as with bicuculline, but they were statistically significant nonetheless. The mechanism for this increase in the rate of adaptation is not clearly apparent from the data.

The effects of bicuculline and phaclofen on the selectivity of the adaptation

Many models of direction selectivity require inhibitory connections either between subregions of a cell's receptive field or between cells with opposing direction selectivity which increase the selectivity of weakly direction selective cells. The present data appear supportive of this idea as the direction selectivity of most cells studied (as defined by the ratio of the preferred to the nonpreferred direction responses) declined with BMI. However, the changes in direction selectivity produced by bicuculline may not necessarily result from a decrease in the inhibitory interactions within the receptive field. Rather they could result from the firing rate in both the preferred and nonpreferred direction responses increasing to a ceiling level. In many cells the application of bicuculline increased both the preferred and nonpreferred direction responses. With high ejection currents of bicuculline, the preferred and nonpreferred direction responses both increased to approximately the same level. One possibility is that the bicuculline increased the responses in a nonspecific way until a ceiling was reached and the preferred direction response could not be increased further. The nonpreferred direction response continued to increase until it too was firing at the same ceiling as the preferred direction response. Cells which originally showed specific adaptation of the preferred direction responses showed nonspecific adaptation when the nonpreferred direction responses were elevated above the asymptotic level of the preferred direction responses. One way to test this hypothesis that BMI increased the responses in a nonspecific manner would be to use suboptimal stimuli (either lower contrast or different spatial frequencies) which would elicit responses well below the ceiling for the cell. Using
lower concentrations of BMI, it would be possible to examine the responses of the cell over a longer periods of time while examining the changes in responsivity. It is likely that the BMI will increase the responses to all the stimuli by a constant ratio consistent with the known role of the GABA-A receptor actions but that adaptation will have a separate effect on the responses which may demonstrate a selectivity for the features present in the adapting stimulus.

In summary, there are two types of inhibitory effects on neocortical neurons. The first is a general hyperpolarizing current which moves the membrane potential closer to the equilibrium potential for Cl⁻ but has relatively little effect on the resistance of the cell (Berman, Douglas, Martin, & Whitteridge, 1991). The second mechanism involves large conductance increases which locally shunt the excitatory inputs. The effects of bicuculline on the visual cortical cells in this thesis appear to be the result of the reduction of the second mechanism since there was a proportional increase in the response of the cell to all stimulus conditions.
Chapter 7
General discussion

One major conclusion of this thesis is that adaptation is not due to a global change in the cell, such as a change in the resting potential or spike threshold. The adaptation of cortical cells can be highly specific for receptive field position as well as direction of motion. Rather the adaptation effects must be localized to specific synapses or dendritic branches of the cortical cell. For example, the adaptation of an ON region of a simple cell does not usually result in reduced responsivity in the neighboring OFF regions. Indeed, sometimes the adaptation may spread to only a fraction of the cells ON region of the receptive field. A second piece of evidence is the asymmetry of the spread of adaptation which related to the direction selectivity of the cells. Strong excitation in a simple cell's receptive field is induced by preferred direction stimulation while inhibition is induced by nonpreferred direction stimulation (Chapter 4). The simultaneous adaptation of excitatory and inhibitory interactions within the cells receptive field is further support for a highly local mechanism of adaptation.

Similar conclusions could be reached based on the results of Vidyasagar (1990) who showed that the application of glutamate alone did not result in adaptation effects. Glutamate is an excitatory amino acid which has been shown to elevate responsivity in almost all cortical neurons (Nicholls & Attwell, 1990). Vidyasagar found the effects of glutamate to be similar to those of bicuculline (also shown here) where the spontaneous and evoked activity both increased dramatically but activation of the postsynaptic cell alone using glutamate did not result in an adaptation of the responsivity. Vidyasagar (1990) showed that prolonged GABA application did not alter the adaptation of cells to prolonged visual stimulation. He argued that the
application of GABA would protect the cell from adaptation. However this does not rule out a purely presynaptic mechanism or a postsynaptic mechanism which is localized to the distal dendrites or even localized to within the postsynaptic dendritic spine. The application of GABA would cause more hyperpolarization of the soma than in the distal dendrites (Berman et al., 1991; Dehay, Douglas, Martin, & Nelson, 1991; Douglas & Martin, 1991; Douglas, Martin, & Whitteridge, 1991). The same could be said of glutamate application which could be acting on synapses within a small range around the pipette or predominantly on the soma.

Adaptation of cells in the visual cortex could result from adaptation of the cells in either the LGN or the retina which project to those cortical receptive field subregions, but we can rule that out because the adaptation effects spread asymmetrically within a subregion and can show interocular transfer in binocular cells.

These arguments rule out a number of possible mechanisms of adaptation, such as a change in the spike threshold or a change in the inhibition directed at the cell body. Therefore, the locus of adaptation must be earlier— but not earlier than the synapses of the LGN afferents onto the dendrites of the visual cortical cells because the cells in the LGN and the geniculate afferents themselves do not show adaptation at the temporal frequencies for which cortical cells adapt. This leaves a number of possibilities which could account for adaptation effects which must be localized to the presynaptic terminal or the distal dendrites of cortical cell. The remainder of the discussion examines a number of these possible mechanisms.

**Presynaptic mechanisms**

A highly localized adaptation effect could indicate a depletion of neurotransmitter at synapses which are highly active. A presynaptic mechanism for
adaptation could explain the localized effects of adaptation of small regions within
the receptive field but additional circuitry is required to explain the asymmetric
spread of adaptation and the direction specific adaptation effects observed in Chapter
2. An adaptation of a tonic inhibitory input from the adapted receptive field position
to other receptive field positions could explain the facilitation of responses at
receptive field positions on the nonpreferred direction side of the point of adaptation.
This adaptation of an inhibitory input could also be the result of transmitter depletion
of an interneuron which is involved in direction selectivity. This inhibitory
interneuron would be adapted even more if the adaptation was the result of
prolonged nonpreferred direction smooth motion. One way to test the presynaptic
depletion hypothesis would be to use a glass recording electrode with an additional
barrel filled with an electron dense staining solution. During a prolonged period of
adaptation, the stain could be injected into the region of the cortex which is being
stimulated. The area of the cortex could then be examined using an electron
microscope to see if there were fewer synaptic vesicles in the presynaptic terminals
at excitatory synapses.

Presynaptic control of transmitter release

It is possible that the level of neurotransmitter released from the presynaptic
terminal is not depleted but is prevented from being released. There is evidence that
a number of presynaptic receptors control transmitter release. Serotonin for example
has been shown to facilitate transmitter release by inactivating potassium channels
(Andrade, 1987). In the mammalian cortex there is evidence that the effects of
serotonin, noradrenalin and acetylcholine are inhibitory on presynaptic terminal
transmitter release (Antonelli, Caciagli, Lambertini, 1984; Bear & Singer, 1986; Collins, Probert,
Anson, & McLaughlin, 1984; Dennis, Curet, Nishikawa, & Scatton, 1985; Foehring et al., 1989; Gean
NicoU, 1982; Scatton, Zivkovic, Dedek, 1982; Schwindt et al., 1989; Schwindt et al., 1988a; Storm, 1990; Suzdak & Gianutsos, 1985a; Suzdak & Gianutsos, 1985b; Suzdak & Gianutsos, 1986; Erdelyi & Such, 1989; Gean & Shinnick, 1989; Goh & Pennefather, 1987; Partridge, 1980; Raiteri et al., 1990; Schwindt et al., 1989; Stafstrom et al., 1984; Storm, 1990).

A logical presynaptic mechanism of adaptation involving modulation of neurotransmitter release would involve the presynaptic GABA-B receptor and therefore Wilson's feedback inhibition model (Wilson, 1975). There are presently three known action mechanisms of GABA-B receptors. Activation of presynaptic GABA-B receptors results in increased potassium currents and decreased calcium currents via ionotropic actions, while the third mechanism involves metabotropic GABA-B receptors which modulate calcium entry into the presynaptic terminal by reducing the phosphorylation of a specific voltage-dependent calcium channel (L-type) (Szekely, Barbaccia, and Costa, 1987; Wojcik, 1986). Agents which specifically block voltage dependent calcium channels also block transmitter release (Szekely, Barbaccia, and Costa, 1987; Wojcik, 1986). Although the experiments in part 3 of the thesis were undertaken to investigate the role of GABAergic inhibition in the adaptation of cortical neurons, we did not investigate the involvement of presynaptic GABA-B receptors. Phaclofen has limited actions on presynaptic GABA-B terminals and blocks the activation of the postsynaptic slowly-inactivating potassium channels which give rise to the slow-afterhyperpolarization. The effects of phaclofen on the presynaptic terminal are only observed at very high concentrations where the actions are thought to be nonspecific. Therefore, further experiments with the selective presynaptic GABA-B antagonists saclofen or CGP-35348 would be useful. One encouraging finding in support of this hypothesis is that saclofen has been shown to abolish the frequency dependent attenuation of EPSPs and tonic spontaneous GABA release by blocking presynaptic GABA receptors on excitatory and inhibitory
terminals, respectively.

**Postsynaptic mechanisms**

Although not conclusive, the effects of BMI on the time constants of adaptation suggest the involvement of postsynaptic events in the adaptation of visual cortical cells. The recent results of Douglas and Martin (1991) showed that the application of bicuculline resulted in a broadening of the EPSP in neurons in cat visual cortex. In addition to, or as a consequence of this bicuculline effect, the magnitude and duration of the sAHP increased. Douglas and Martin (1991) suggested that the blockage of the GABA-A receptor allows the membrane potential to move closer to the GABA-B potassium-mediated reversal potential. Although there are a number of possible postsynaptic mechanism which would explain the data obtained in this thesis, I favor a mechanism involving either potassium channel activation or a mechanism which controls the amount of intracellular calcium. Indeed if I were to continue these experiments, I would systematically investigate these two possibilities.

**Potassium channel activation as a mechanism of adaptation**

The duration or size of the EPSP determines the duration and magnitude of the Ca(2+)-dependent potassium slow after-hyperpolarization. By increasing both the duration and the size of the EPSP the amount of Ca(2+) entering the cell increases and the number of Ca(2+)-dependent potassium channels open at any one time is also increased. This interpretation could also explain the results of bicuculline on the time course of adaptation observed in chapter 6, if the effect of repetitive stimulation is to activate the slowly inactivating hyperpolarizing K+ current. If the magnitude of the sAHP increased with repeated stimulation, then increasing the EPSPs with bicuculline would increase further the magnitude and duration of the sAHP. This intracellular inhibition would then slowly build and would outlast the short duration
excitation. It is possible that the iontophoresis of phaclofen in the present experiments did not adequately block a sufficient number of postsynaptic GABA (B) receptors and so a strong hyperpolarizing current was activated by repeated stimulation. Another possibility is that the adaptation results from a nonGABAergic inhibitory transmitter which also increases potassium conductance. Adenosine has been shown to increase potassium conductance in cortical cells and this effect is blocked by barium which suggests that like GABA-B, adenosine acts via the slowly inactivating potassium channel on the postsynaptic terminal. Recently, it has been shown that adenosine is produced from the cAMP which is released from the astrocytes in cortical cultures following stimulation of the beta-adrenergic receptor (Petrison, Knowles, & Rosenberg, 1991). It is possible that a similar mechanism exists in the visual cortex in either astrocytes or in neurons themselves such that with repeated stimulation the concentration of cAMP and adenosine in the extracellular space around active terminals increases. This buildup of the inhibitory transmitter adenosine could result in a decrease in the release of transmitter at the active presynaptic terminal and possibly at afferent terminals within a limited range around the active site. This would account for the limited spread of interocular transfer of adaptation (Chapter 2).

Calcium-dependent mechanisms of adaptation

Calcium has been shown to be critically important in the light-adaptation process in the retinal photoreceptor. Calcium has an inhibitory effect on the cGMP content at the outer segment of the photoreceptor which results in the cGMP-gated Na++ channel closing and a hyperpolarization of the cell. The function of this light adaptation is thought to be to control intracellular calcium or to reduce the background noise associated with fluctuations in the normal cGMP metabolism (Yau,
A similar mechanism could operate in the cells in area 17 to control either presynaptic transmitter release or postsynaptic activity using either cGMP-gated sodium or calcium channels or potassium channels. A number of calcium-dependent potassium channels have been described which have higher open time probabilities at high intracellular calcium concentrations. However, it is not necessarily the calcium itself that triggers these potassium channels to open. One recently discovered potassium channel is sensitive to ATP levels. During maintained depolarization the levels of ATP drop triggering the $K_{\text{atp}}$ channels to open thereby hyperpolarizing the cell. $K_{\text{atp}}$-channel agonists such as cromakalim can induce hyperpolarization in a neuron and inhibit elevated calcium concentrations (Chisholm, Davis & Hunnicutt, 1991).

A critical event in a cell's postsynaptic response to excitatory neurotransmitters is the increase in calcium entry into the cell and the release of calcium from intracellular stores (endoplasmic reticulum and mitochondria) (Artola, Brocher, & Singer, 1990; Artola & Singer, 1987; Artola & Singer, 1990; Coan, Irving & Collingridge, 1989; Davies, Starkey, Pozza & Collinridge, 1991; Komatsu & Toyama, 1989; Tsumoto, Kimura, Nishigori, & Shirokawa, 1989). In some cells, calcium itself can act as a second messenger, activating specific enzymes such as protein kinase. These intracellular events can alter the excitability of the cell or allosterically change the receptor thereby changing its function. However, very high concentrations are excitotoxic and result in neuronal death (Collins & Olney, 1982; Kauppinen, McMahon & Nicholls, 1988; Zeewalk, Hyndman & Nicklas, 1989; Zeewalk & Nicklas, 1989). The modulation of neuronal excitability in adaptation may serve to limit the amount of calcium inside the cell. Or alternatively, the amount of calcium may serve to control neuronal excitability for a yet undetermined function. Calcium concentrations can be measured during excitatory and inhibitory events in cultured neurons using fluorescent dyes such as Fura-2 (Kauppinen et al, 1988). May, Decoster & Tortella (1991) found that calcium
influx during glutamate stimulation can show three distinct patterns in primary rat cortical neurons: a fast transient response; a delayed sustained response; and a response which appears to be the result of both of these processes. The decay of the calcium following the transient response shown by May et al. (1991) appears to have a time course similar to that of adaptation in neurons in area 17 of the cat. The calcium reaches its peak concentration in the cell within a few hundred milliseconds and then decreases over 60 to 90 seconds. Despite the continued application of glutamate the calcium concentration did not increase again until the glutamate was removed and the cell was allowed to recover. Alternatively the cells which showed a delayed calcium response to glutamate did not show a decrease in calcium concentrations while the glutamate was being applied.

By measuring the calcium concentration in a cell before, during and after adaptation using brain slice techniques it would be possible to determine if the changes in the responsivity associated with adaptation are correlated with changes in the calcium concentrations in the cell. However, with most calcium imaging techniques it is not possible to examine the concentration in the distal dendrites or in the spines and so the usefulness of this technique may be limited.

*The function of adaptation in the visual system*

An possible role for adaptation is one similar to that of habituation such that the cells responses to constant stimuli are reduced. Although the term constant stimuli usually refers to stationary patterns or illumination levels, to a cortical feature detector a constant stimuli could be a stimulus of a particular orientation, spatial frequency and velocity. Adaptation and habituation share many common properties including the importance of stimulation rate and intensity, they are thought to be different processes (Byrne, 1982; Castellucci & Kandel, 1974; Cawthorpe et al., 1988; Gingrich &
Byrne, 1985; Hernández-Peón et al., 1958; Rankin & Carew, 1987). The behavioral and physiological effects of habituation of the Aplysia results from either a transmitter depletion or immobilization. Dishabituation and sensitization are thought to have a common mechanism and involve the presynaptic facilitation of transmitter release by serotonin (Belardetti et al., 1983; Boyle et al., 1984; Braha et al., 1990; Glanzman et al., 1989; Hammer et al., 1989; Klein & Kandel, 1980; Ocorr et al., 1986; Pollock, Bernier, & Camardo, 1985). The cells in the visual cortex do not show dishabituation to a novel stimulus but the function of adaptation may be the same. In the visual cortex there are a great many cells which have different firing frequencies and are selective for different features and therefore the need to have presynaptic facilitation of habituated responses may not have developed in the visual cortex. Furthermore, the need to dishabituate an adapted response may be linked more to the direct behavioral output of the adapted cells. Since the cells in the visual cortex are not directly responsible for a motor response they may not have the mechanisms necessary for dishabituation.

Adaptation may control the postsynaptic response so as to decrease the noise associated with spontaneous or weak signals. A number of cortical circuit theories suggest that excitatory feedback within the cortex results from a relatively weak geniculate input. However, with increased excitation a cell's response to weak stimuli are also elevated. Adaptation may reduce the level of excitation within the network while allowing the reciprocal excitation to continue thus increasing the signal to noise ratio of the cells response to a particular stimulus. However, the results of psychophysical experiments suggest that adaptation results in a decrease in sensitivity to the adapting stimulus rather than an increase suggesting that adaptation does not serve to increase the signal to noise of a network of cells. Alternatively, this decrease in the responsivity may serve to increase the dynamic range of the responses of the cells in a network. If the cells are firing at the upper limit of their dynamic range then there is no way to discriminate between stimuli of supra-
threshold contrasts. By reducing the responses of the network to that stimulus (as during adaptation) the cells in a network can theoretically respond differently to stimuli which are of a higher contrast or for which the cell's tuning is more suited (Dean, 1983; Ohzawa et al, 1982,1985).

Adaptation may protect the cells from the pathogenic effects of high concentrations of glutamate (Benveniste et al., 1989; Ikeda, Nakazawa, Abe, Kaneko, & Yamatsu, 1989; Lobner & Lipton, 1990; Lust et al., 1988; Nielsen et al., 1989). In normal activity, adaptation may serve to limit the release of glutamate or other excitatory amino acids, or other postsynaptic actions, during high-frequency repeated stimulation when such stimulation would result in a buildup of glutamate in the extracellular space around the synapse or substances within the cells which would be toxic to the cell at high concentrations. Only those cells which are most sensitive to the adapting stimulus would be at risk and so the adaptation aftereffects would be specific for those cells which were greatest stimulated. Although bicuculline alone did not result in adaptation, bicuculline concurrent with repeated stimulation increased the rate of adaptation. The bicuculline increased the spontaneous and stimulus evoked activity of the cells and in some cells the bursting patterns approached epileptiform activity.

Adaptation appears to be a process present in all types of visual cortical cells as well as cells in other visual areas (Albrecht et al (1984); Hammond & Mouat (1988); Hammond, Mouat, & Smith (1988); Hammond et al (1985); Hammond et al (1986); Hammond et al (1989); Marlin et al (1988); Marlin et al (1987); Petersen et al (1985); Saul & Cynader (1989a); Saul & Cynader (1989b)). There are no differences between the cells in layer 4 or the cells in the upper or lower layers in the amount of adaptation observed. Although not all cells showed the same time course for adaptation, these differences were not systematically related to the location of the cells in the cortex. However, simple cells
show greater direction selective effects while complex cells show greater variability. This may be related to the pattern of afferent inputs, the degree of tonic inhibitory input or the amount of excitatory feedback within a cortical network. The variability in the responsivity could be reduced with adaptation. Although the responses of single cells are highly variable, the ability of the visual cortex to respond to a stimulus is much less variable. The networks of cells which give rise to our perceptions cooperate to develop a clear picture of our external world. It is only when the performance of these cells is compromised, as with adaptation, that our normal perceptions are altered. The high degree of similarity between the aftereffects observed psychophysically and the changes in the responses of single cells in the visual cortex suggests that it is the sum of the changes in the neuronal activity that mediates the perceptual aftereffects. Single cell recording has some limitations which may be important for understanding the mechanisms of adaptation. If adaptation was the result of a cooperative network, then recording the responses of a single cell may not help understand the phenomenon. Alternatively, if the mechanism of adaptation is the result of an intrinsic cellular process, then extracellular recording from a single cell may not be as informative as intracellular recording. However, using extracellular single cell recording, we determined the specificity of adaptation for location in the receptive field. We also applied antagonists of the neurotransmitter GABA to test the hypothesis that an inhibitory GABAergic input mediated adaptation. An even better technique which we are presently attempting to set up in our lab is in vivo intracellular recording such as employed by Douglas et al. (1991) which allows the use of iontophoresis, electrical and visual stimulation while recording the action potentials and the postsynaptic responses (EPSPs and IPSPs) of single cells in the visual cortex. However, this technique is extremely difficult and the number of cells which can be examined is much less than with extracellular recording. As a result, in a smaller sample of cells
it is possible to understand the ionic events which are associated with a cell's responses to a natural stimulus. Intracellular recording using brain slices can also be used to examine the responses of single cells and is not as technically difficult as intracellular recording in vivo. Using electrical stimulation of the afferent fibers it is possible to mimic the activity of the cell's responses to light in vivo. An added advantage to intracellular recording is the decrease in variability associated with a constant stimulus. The ability to analyze analog data would greatly improve the reliability of the cells and the number of trials necessary would decrease.

Although some progress has been made in the localization and the elimination of some possible mechanisms of adaptation using the extracellular methods available, it is clear that to determine the mechanism(s) of adaptation in visual cortical cells we must examine the responses using intracellular recording techniques and single channel recordings. However, like extracellular recording, intracellular recording techniques are biased to somatic events. Therefore, to clearly define adaptation as a pre or postsynaptic event it may be necessary to record simultaneously from the presynaptic terminals of one cell and the dendritic branches of the cells it synapses with.
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