NEURAL MECHANISMS UNDERLYING OBJECT SELECTIVITY IN MACAQUE INFEROTEMPORAL CORTEX

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The inferotemporal cortex of the macaque monkey mediates the recognition of objects in the visual world. The purpose of the research presented in this dissertation was to investigate the neural mechanisms underlying two poorly understood aspects of object recognition. The first experiment addressed the question of how visual features are integrated in IT. In this study, we sought to determine whether feature selectivity for shape and color is integrated by IT neurons via a conjunction-coding mechanism, or via linear summation. We demonstrate that visual responses of most IT neurons encode shape and color information in a linear manner. Our results shed light on the computational strategy that the brain employs to construct a versatile representation of the visual world.

The purpose of the second experiment was to investigate the neural mechanisms underlying repetition priming. Repetition priming is a form of rapid visual learning, whereby previous experience with an object allows for faster, more efficient perceptual processing of that object upon subsequent encounters. This behavioral process is believed to be dependent on activity reductions in single IT neurons, but this hypothesis has never been tested. Indeed, repetition priming has never been demonstrated before in monkeys. To address this issue, we adapted the experimental paradigm of repetition priming for use in primate physiology. We demonstrate that repetition priming at the level of behavior is accompanied by repetition suppression at the level

of single neurons in IT. We further demonstrate that repetition suppression in IT results in a proportional scaling reduction of visual responses, and not in a sharpening of the stimulus selectivity. These findings constrain the possible mechanisms whereby visual response plasticity in IT could contribute to behavioral priming.

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PREFACE

The opportunity to express our gratitude to those who have enriched our lives comes along all too infrequently, and so I'm pleased that completing this dissertation provides the opportunity to do just that. My years in Pittsburgh have been truly formative, and it's been a pleasure and an honor to join this neuroscience community. My thanks to all who made it possible for me to come here initially, and to those who made the experience so memorable and rewarding. To begin with, I'm extremely fortunate to have entered the field by joining Paul Brelin's lab at the Monell Chemical Senses Center in Philadelphia. Working with Paul led me to appreciate the value of good colleagues and mentors, and was instrumental to my subsequent arrival in Pittsburgh. I had the good fortune to join the Department of Neuroscience and the CNBC thanks to German Barrionuevo, who encouraged me to apply to Pittsburgh and welcomed me into his lab during my first two and a half years here. I can't imagine training in a more stimulating and collegial environment, and I admire Ed Stricker, Jay McClelland, and Alan Sved for having the vision and the perseverance to make it a reality.

It was clear from the moment I encountered Joan Blaney's preparations for my interview in Pittsburgh that this was a remarkable graduate program. That first impression has been borne out constantly over the past eight years. With regard to acquiring a technical and conceptual grasp of experimental physiology, Nathan Urban, Darrell Henze, Guillermo Gonzales-Burgos, Floh Thiels, Karen Medler, Julie Rollenhagen, Chris Baker, Karen McCracken, Matt Roesch, and Kae Nakamura were extremely helpful during the early stages. More recently, Marc Sommer, Matt Smith, and Charlotte Taylor, and Steve Gotts have offered invaluable advice during the

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My dissertation committee members, German Barrionuevo, Marlene Behrmann, Carol Colby, Mike Lewicki, and Rafi Malach, have offered invaluable advice and criticism during the preparation and defense of this document, and I thank them for being so generous with their time and expertise. Dr. Malach's work obviously inspired much of my own research, and I'm honored that he was willing to join my committee as the external examiner. All the experiments that were described in this thesis (plus a few others that weren't) were conducted in collaboration Carl Olson, and those aspects of the work that are elegant and admirable reflect his influence. I'm grateful to him and to Carol Colby, my dissertation committee chair, for making this work possible. May their intellectual rigor and creativity also be reflected in my future scientific endeavors.

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1. General Introduction

1.1. Overview

The ability to recognize visual objects is one of the most remarkable faculties of the human brain. Throughout the day, we rely on our visual systems to discriminate among the welter of images that impinge on the retina. Despite the fact that a new visual world must be apprehended with each eye movement, the brain is capable of rapidly distinguishing between a swimming pool and a teacup, a tangerine and a basketball, and the faces of friends and strangers. Survival occasionally demands that subtle features of visual objects be perceived with a high degree of accuracy and speed. How is object recognition accomplished by the brain? Although the gross brain regions that contribute to this process have been identified, the precise neural mechanisms that mediate object perception are not well understood.

The goal of this introductory chapter is to briefly review the current state of our knowledge of the neural mechanisms underlying object recognition. We will focus primarily on the visual system of the macaque monkey, with the aim of highlighting some critical gaps in our current understanding. We will conclude this chapter by identifying a set of specific experimental aims that address these gaps. In chapter 2, we describe the results of an experiment designed to investigate the principles of feature representation. In chapter 3, we describe the results of an experiment designed to investigate the relation between neural activity and behavior in short-term visual learning. Finally, in chapter 4, we will conclude by assessing how the results of

these experiments have furthered our understanding of the neural mechanisms of object recognition.

1.2. Organization of the primate visual system

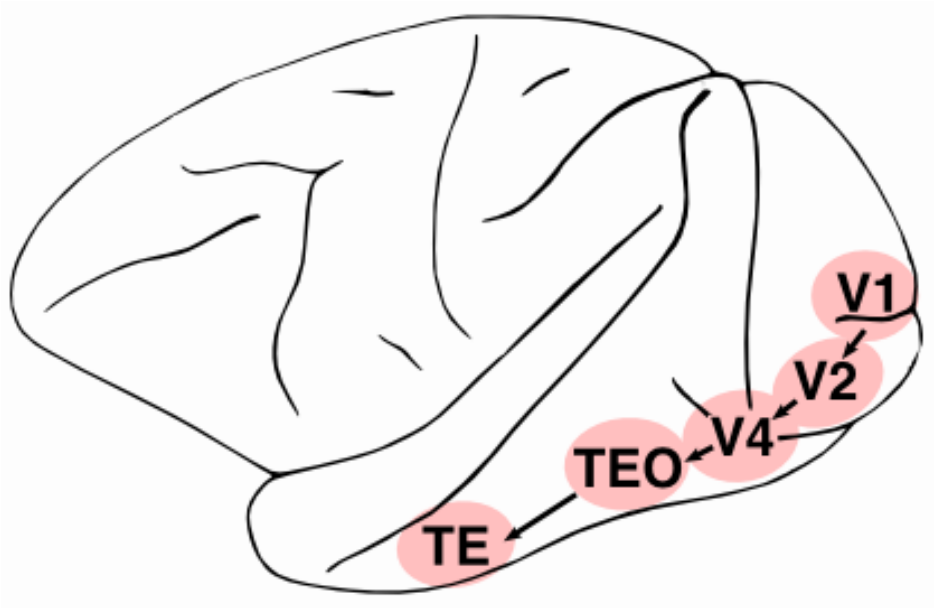


Figure 1. Diagram of the ventral processing pathway in the macaque monkey brain. Shaded regions indicate the location of each area. Arrows indicate the direction of feed-forward transmission of sensory input from primary visual cortex (area V1) to inferotemporal cortex (areas TEO and TE).

An extremely large portion (approximately 55%) of the macaque cerebral cortex is dedicated to vision (Tootell et al 2003). A preponderance of evidence from neuropsychological, anatomical, and physiological studies have established that the primate visual system is organized into two major processing pathways (Ungerleider and Mishkin 1982). The dorsal, or "where" pathway, is

dedicated to processing spatial information about the visual world, whereas the ventral or "what" pathway mediates the recognition of visual objects (Figure 1). The initial evidence for the functional specialization within dorsal and ventral pathways came from lesion studies in monkeys. Monkeys with lesions to posterior parietal cortex are impaired on performance of tasks that require evaluating the spatial relation among several objects, but perform normally in pattern discrimination tasks (Pohl 1973). Conversely, monkeys with lesions to inferotemporal cortex display the opposite pattern of impairments (Iwai and Mishkin 1968, Cowey and Gross 1970). Anatomical tract tracing studies have revealed that visual information reaches posterior parietal cortex via a succession of projections originating in striate, or primary visual cortex (V1), and proceeding through the pre-striate areas V2, V3, and MT. The ventral pathway originates in area V1 and culminates in inferotemporal cortex, which is the highest level of the "what" pathway dedicated to exclusively visual stimuli.

1.3. Principles of object encoding in the ventral visual pathway

Hierarchical stages of visual processing: early stages.

The ventral cortical visual pathway begins in primary visual cortex (V1), progresses through extra-striate visual areas V2 and V4, and finally terminates in the areas TEO, TE, and perirhinal cortex which together constitute the inferotemporal cortex (IT). The processing within the ventral stream is governed by four organizing principles. First, the early stages of the pathway, V1 through V4, are retinotopically organized, in that neurons that respond to stimuli in a given area of visual space are arranged in a predictable spatial arrangement in the cortex (Ungerleider

and Desimone 1986, Desimone and Ungerleider 1989, Brewer et al 2002). Second, all visual areas send projections to, and receive reciprocal projections from, the adjacent visual areas (Desimone and Ungerleider 1989, Felleman and van Essen 1991). Third, visual areas also send skip-ahead projections beyond their immediate neighbors, and, in turn, receive projections from those same areas, although the density of interconnections decreases as the level of separation between areas increases (Nakamura et al 1993). Fourth, the properties of visual stimuli that are effective in driving neurons located at later stages of the visual hierarchy become progressively more subtle and difficult to characterize (Gross et al 1972, Tanaka et al 1991).

A general principle that results from this hierarchical arrangement is that visual stimuli are represented at a progressively higher level of abstraction at each successive processing stage. In the early stages of the ventral pathway, neural activity is dedicated to constructing an efficient, veridical representation of the visual scene. In the later stages, neural activity is dedicated to constructing a high-level representation of the objects that are present in the visual scene. We consider how the visual system achieves this transformation in the following sections.

Area V1.

Primary visual cortex, also known as V1 or striate cortex, is the earliest cortical stage in the ventral processing stream. The status of striate cortex as a primary sensory area is established by the fact that it receives direct projections from the primary thalamic visual area, the lateral geniculate nucleus, and consequently is only a single synapse removed from the output of the retina (Malpeli and Baker 1965). Neurons in V1 are sensitive to color (Komatsu 1998) and to luminance contrast at a specific orientation and spatial frequency (Hubel and Wiesel 1959, Hubel

and Wiesel 1968). Relatively simple models can account for a great deal of variance of activity in V1 neurons by positing that V1 receptive fields act as linear filters for stimulus energy at a specific orientation and spatial frequency (Reid et al 1987).

Linearity is an important property that many neurons in V1 possess (Figure 2). Because spatial summation within V1 receptive fields is linear, the visual responses of V1 neurons can be predicted for a wide range of patterns of sensory stimulation by observing the responses to a comparatively small set of images. Linearly independent integration of stimulus energy by V1 neurons makes it possible to characterize the cell's response properties in an automated and highly efficient manner by using a method known as reverse-correlation analysis (Reid et al 1992). Accordingly, a great deal is has been learned about the representation of the visual scene in the earliest stage of cortical processing.

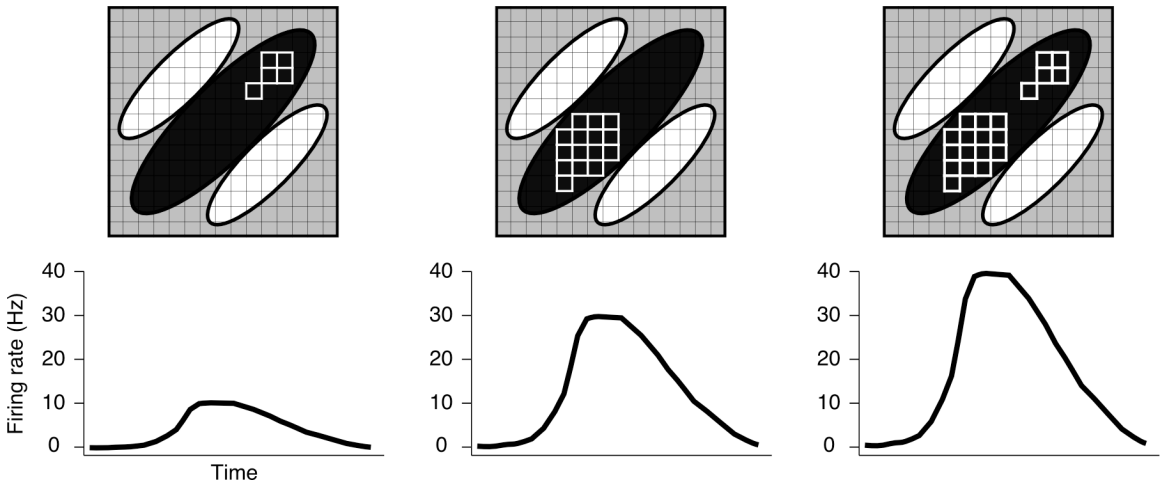


Figure 2. Example of linear stimulus integration in a hypothetical V1 simple cell. Upper panels: The receptive field of a V1 simple cell has "ON" and "OFF" sub-regions (illustrated as black and white ellipses, respectively). Lower panels: The firing rate evoked by visual input is proportional to the spatial extent of stimulation that falls within the neuron's ON sub-region. Thus, the neuron's response to 15 illuminated pixels (right) can be predicted by observing the neuron's response to 5 and 10 pixel stimuli presented separately.

Progress in understanding the role of V1 under ecologically relevant conditions has come from measuring the response parameters (primarily orientation and spatial frequency) of a large number of V1 neurons. By comparing the distribution of these parameters to the statistics of natural scenes, computational modeling studies have demonstrated that a representative population of V1 neurons is suited for encoding the structure of natural images in an optimally efficient manner (Olshausen and Field 1996, Lewicki and Olshausen 1999). A major avenue of current research in early visual system physiology focuses on how well the parameters of V1 receptive fields measured with reduced stimuli can predict the activity of V1 in response to more complex patterns of visual stimulation. Research in this vein has revealed that V1 neurons sensitive to highly localized visual context, in the form of visual stimulation outside the classical receptive field (Knierim and van Essen 1992, Vinje and Gallant 2000). Such effects may emerge

from lateral projections between cells within V1, but are probably due at least in part to feedback projections from higher order visual areas. Further insight into the network mechanisms that contribute to context integration can be gained by examining the time-course of selectivity. For instance, the initial phase of the visual response of V1 neurons is not sensitive to higher-order contextual information that influences the interpretation of the retinal image at a global level (Zhou et al 2000, Rossi et al 2001, reviewed by Albright and Stoner 2002). However, the later phases of visual responses from V1 neurons do reveal some sensitivity to global context. The late emergence of these signals suggests that they derive from higher visual areas (Lee et al 1998).

Area V2.

Consistent with the role of primary visual cortex discussed above, lesions to V1 result in a severe inability to detect low-level visual features, such as orientation of lines defined by luminance contrast in the area of visual space that corresponds to the lesion site. By comparison, monkeys with V2 lesions are relatively unimpaired in discriminating lines defined by contrast edges, but their perception for line segments defined by texture cues is severely impaired. V2 lesions also impair perception of line segments that require interpreting discrete dots as being grouped together on the basis of proximity and collinearity (Merigan et al 1993). Physiological properties of V2 neurons initially appear to be very similar to V1. The receptive fields are only slightly larger (on the order of 1.5 dva, Kobatake and Tanaka 1994). Although many V2 neurons respond preferentially to stimuli that include curved elements or angular junctions, most V2 neurons can be driven by oriented bars and grating patterns in a manner similar to V1 neurons (Hedge and van Essen 2000). However, V2 neurons are more sensitive to higher level features

of the visual scene, which require some degree of interpretation. Most notably, V2 neurons are far more sensitive to illusory contours, which are implied by the global structure of a visual image but are not explicitly present as luminance contrast-defined edges (von der Heydt et al 1984). V2 neurons are also sensitive to boundary ownership effects (Zhou et al 2000). Although V1 neurons also show some sensitivity to global context (such as illusory contours and boundary ownership) in the later phase of evoked visual responses, this modulation is usually attributed to feedback projections from higher level visual areas (Lamme 1995, Lamme and Roelfsema 2000, Super et al 2001, Lee et al 1998, Lee et al 2002). Thus, originating in V2 we see the beginnings of the construction of a higher-order interpretation of the visual scene, rather than an efficient replication of the scene.

Area V4.

Neural activity in V4 reflects a far greater degree of complexity than what is observed in earlier areas. Receptive fields are many times larger (5.5 dva on average, Kobatake and Tanaka 1994). Concomitant with increased receptive field size, V4 neurons respond to stimuli with greater complexity than is commonly found in V2 (Kobatake and Tanaka 1994). In addition to being selective for visual stimuli, V4 neurons are strongly modulated by the visual context in which those stimuli are embedded. For example, the effects of boundary ownership that were first evident in V2 are both stronger and more common in V4 (Zhou et al 2000). Also, the responses of chromatically tuned V4 display the property of color constancy (Zeki et al 1983a, Zeki et al 1983b). Color constancy refers to the fact that, in human subjects, color perception is robust over a wide range of ambient lighting conditions. This perceptual ability is remarkable,

considering that the wavelength of light reflected from surfaces depends strongly on the chromaticity of ambient illumination.

In addition to processing contextual information in the visual scene, V4 also plays an important role in visual attention. While monkeys with V4 lesions are only minimally impaired at discriminating the orientation of grating stimuli, their attentional focus is easily disrupted by the presence of distracting stimuli. This result indicates that V4 is necessary for focusing spatial attention in the presence of distracting stimulation (De Weerd et al 1999). Spatial attention has a profound effect on visual responses in V4 neurons (Moran and Desimone 1985, Motter 1994, Connor et al 1996, McAdams and Maunsell 1999, Reynolds and Desimone 2003). This attentional modulation, which is subtle in V2 and virtually absent in the visual responses of single neurons in V1 (Luck et al 1997, Marcus and van Essen 2001), is likely attributable to the very large suppressive surrounds of V4 receptive fields (Desimone et al 1985). Thus, V4 is the first stage of the ventral processing pathway that marks the transition from low-level sensory processing to higher-level cognitive processing. The role of cognitive factors in object representation becomes more pronounced in the inferotemporal cortex, the region that receives the majority of feed-forward projections from V4.

1.4. High-level object representations in inferotemporal cortex

Distributed coding of object features.

Neuropsychological studies provided the first evidence that IT plays a crucial role in the representation of visual objects. Monkeys with IT lesions display severe deficits in visual pattern recognition (Kluver and Bucey 1937, Iwai and Mishkin 1968, Cowey and Gross 1970; reviewed in Dean 1976). Early physiological recording studies established the fact that IT neurons are driven by exclusively visual sensory stimuli (Gross et al 1972), and tend to be driven strongly by complex visual stimuli (Gross et al 1969, Gross et al 1972, Desimone et al 1984, Tanaka et al 1991). Presumably, the pattern of visual responses observed in IT neurons constitutes a representation of a visual object in some high-dimensional feature space (Plaut and Farah 1990). However, the general principles of the coding scheme employed by IT have remained elusive, because visual responses in IT have proven difficult to characterize in a systematic and objective manner. The challenge of identifying the dimensions of stimulus space is made clear by an account of the first single unit recording experiment in IT:

> ... One day when, having failed to drive a unit with any light stimulus, we waved a hand at the stimulus screen and elicited a very vigorous response from the previously unresponsive neuron. We then spent the next 12 hours testing various paper cutouts in an attempt to find the trigger feature for this unit. When the entire set of stimuli used were ranked according to the strength of the response that they produced, we could not find a simple physical dimension that correlated with this rank order. However, the rank order of adequate stimuli did correlate with similarity (for us) to the shadow of a monkey hand (Gross et al 1972).

The selectivity of IT neurons for certain natural objects, such as hands and faces (Perrett et al 1982), superficially suggests a coding scheme based on a correspondence between individual neurons and unique objects (a concept referred to as “pontifical cells”, Sherrington 1955). However, it is more likely that IT instantiates a distributed population coding scheme. Several

lines of evidence support this idea. First, the majority of IT neurons are broadly tuned and will respond in a graded fashion to a large number of stimuli (Young and Yamane 1992, Rolls and Tovee 1995). Second, hand and face cells respond to many different examples of their preferred object (Hung et al 2005, Kreiman et al 2000), indicating a selectivity for categories of objects (e.g., faces) rather than specific individuals (e.g., Abraham Lincoln's face). Third, virtually no neurons in IT respond to their preferred stimuli irrespective of viewing angle (Logothetis et al 1995). Consistent with the interpretation of a population coding scheme, optical imaging experiments reveal that visual stimuli evoke responses in a widely distributed array of discrete patches in IT (Wang et al 1996, Wang et al 1998). In some cases, activity within a specific patch is attributable to a particular stimulus feature (Wang et al 1998). Together, these findings indicate that object representation in IT is not mediated by the convergence of sensory information in specific "pontifical" cells, but rather is based on a broadly distributed coding scheme in which each neuron participates in the representation of many different objects.

Invariance of visual responses.

Thus far we have noted that successive stages of the ventral stream process stimuli at progressively higher levels of abstraction. This trend culminates in IT in neuronal responses that show a great degree of invariance to several types of stimulus transformations. It has been suggested that the large receptive fields of IT neurons are well-suited to contribute to translational invariance (Gross et al 1972, Ito et al 1995). Consistent with this proposal, it has been demonstrated that monkeys with IT lesions have deficits in recognizing that the same object presented in two different regions in the visual field is in fact the same object (Seacord et al 1979). A role for IT in translation invariance is further supported by psychophysical evidence

from a behavioral priming task that priming of object recognition is invariant to translations that are smaller than the size of an IT receptive field, but is abolished by larger translations (Bar and Biederman 1999).

Several studies have also demonstrated that IT neurons maintain their stimulus selectivity over transformations of stimulus size (Desimone et al 1984, Schwartz et al 1983), even over scaling over 4 octaves (Ito et al 1995). More recently, IT neurons were shown to be relatively insensitive to illumination angle, despite the fact that the pattern of shadow cast over an object can have a dramatic impact on the arrangement of luminance within the image (Vogels and Biederman 2002). IT lesions have been demonstrated to impair invariant object recognition over changes in both image scale and in illumination angle (Weiskrantz and Saunders 1984). Taken together, the evidence that IT neurons display such a high degree of invariance suggests a role in invariant object recognition. This degree of robustness to stimulus transformations indicates that processing in IT takes place at a very high level of abstraction, presumably built up over successive stages of inference about stimulus properties, which are based on contextual cues in earlier visual areas.

Influence of attention and awareness on visual responses.

In addition to being highly selective for specific properties of the visual scene, IT neurons are extremely susceptible to modulation by higher-level cognitive influences. Such properties are likely due to the dense interconnectivity between IT and prefrontal cortex (Webster et al 1994). Three lines of evidence establish that the responses of IT neurons cannot be accounted for exclusively by the physical properties of visual stimulus being viewed, but rather are dependent

on the cognitive state of the subject. First, in subjects performing a delayed match to sample (DMS) task, activity of IT neurons reflects the identity of the stimulus the subjects are required to hold in working memory during the delay interval between sample and match (Fuster and Jervey 1982, Fuster 1990, Miller and Desimone 1993, Naya et al 1996; reviewed in Miyashita 1993). Second, IT neurons are known to be strongly influenced by attentional modulation (Chelazzi et al 1998). Finally, evidence from binocular rivalry experiments indicates that activity in IT corresponds to the subject's conscious awareness, rather than what stimulus is present or absent from the visual scene (Sheinberg and Logothetis 1997). Binocular rivalry is an experimental paradigm in which two different images are presented to each eye. Under these conditions, subjects perceive only one of the images at a time, and the other image is suppressed from awareness. Rivalry produces more ambiguous effects in earlier visual areas, with the general pattern that neural activity becomes progressively more correlated with the subjectively perceived stimulus at increasingly higher levels of the ventral visual pathway (Leopold and Logothetis 1996). Subsequent studies conducted in animals searching for a target stimulus embedded in a realistic natural scene under free viewing conditions have demonstrated that neural activity in IT reflects conscious awareness under more realistic conditions (Scheinberg and Logothetis 2001).

Experience dependent plasticity of object representations.

In addition to its connections with association areas in frontal cortex governing executive function, a role for IT in long-term memory is indicated by its dense interconnectivity with the hippocampal formation (Suzuki and Amaral 1994, Saleem and Tanaka 1996). Furthermore, it has been demonstrated that long-term potentiation is more readily induced by high-frequency

stimulation in IT than in early visual cortex (Murayama et al 1997). In addition to reflecting the observer's current mental state, IT neurons are also sensitive to the animal's past history. Much of the evidence for long-term plasticity in IT representations comes from tasks in which animals are trained to associate two different visual stimuli. As a result of paired associate training, IT neurons respond similarly to visually distinct stimuli that the neurons would ordinarily distinguish (Miyashita 1988, Erickson and Desimone 1999). This paired-association learning has generally been studied after extensive training, but some evidence suggests that plasticity is observable over short intervals (Messinger et al 2001). This plasticity in visual representations has been linked to up-regulation of brain derived neurotrophic factor (BDNF) in perirhinal cortex (Tokuyama et al 2000). This neurotrophic factor is specifically implicated in the late phase of long-term potentiation (Korte et al 1998); thus BDNF expression serves as a localizer for recently modified synapses. Long-term changes in synaptic plasticity are presumably responsible for the tendency of neighboring neurons in IT to develop correlated patterns of stimulus selectivity as a result of prior experience (Erickson et al 2000). In a study of long-term expertise training, in which monkeys were required to respond to visual objects on the basis of feature conjunctions, IT neurons were shown to be more selective for the task-relevant object stimuli (Baker et al 2002). These results establish that IT neurons are plastic over long intervals, and that IT representations can change over time.

1.5. How is selectivity for feature components integrated in IT?

On the basis of the evidence reviewed above, there is good reason to believe that activity in IT constitutes a representation of the identity of visual stimuli and mediates object recognition. However, it is not known how information about different features is integrated within this coding scheme, or even what the relevant dimensions of the features space are. In early visual cortex, many neurons are known to integrate spatially distributed patterns of sensory stimulation through a linear summation mechanism. Neurons in IT are generally believed to integrate higher-order stimulus properties though a feature conjunction coding mechanism. However, very few studies have tested this hypothesis directly (Baker et al 2002). The aim of the experiment described in chapter 2 will be to explicitly test whether integration of shape and color selectivity in IT follows a conjunction coding scheme or a linear scheme.

1.6. How are behavior and neural activity influenced by stimulus repetition?

We have reviewed evidence that establishes that (1) activity in IT is highly task-dependent and reflects the animal's current mental state, and (2) responses in IT are highly plastic, in that they are modifiable by prior training and experience. As we will discuss in chapter 3, a functional role for IT has also been proposed in perceptual priming (Desimone 1996, Wiggs and Martin 1998). Repetition priming is a behavioral phenomenon whereby prior exposure to a visual stimulus results in faster or more efficient processing of the same stimulus upon subsequent

exposures. However, it has never been demonstrated that changes in IT activity occur in the context of a behavioral priming task. The aim of the experiment described in chapter 3 will be to test whether stimulus repetition exerts parallel effects on both behavioral and neuronal responses.

1.7. Goals

In summary, it is well established that neurons in IT contribute to visual object recognition. However, it is not clear how the presence of multiple features in a single object is reflected by neural activity in IT. Furthermore, IT neurons are known to be strongly influenced by high level factors related to both the animal's current cognitive state, and to the animal's past experiences.

The experiment described in Chapter 2 focused on how feature selectivity is integrated in IT. To address this issue, we assessed the responses of single neurons in IT to an array of visual stimuli in which the shape and color features were varied independently. The aim of this project was to answer the question: Do the feature dimensions of shape and color affect neural activity in a linearly independent manner?

The experiment described in Chapter 3 focused on how stimulus repetition influences both behavioral and neural responses. To address this issue, we recorded neural responses in monkeys that were performing a symmetry decision task. In the course of this task, monkeys responded to a large set of visual stimuli that were each repeated once. The aim of this project was to answer the following four questions. (1) Do the behavioral responses of monkeys undergo

repetition priming? (2) In the context of a behavioral priming task, do the visual responses of IT neurons undergo repetition suppression? (3) Do the behavioral and neuronal effects of stimulus repetition covary? (4) How does repetition suppression affect the stimulus selectivity of IT neurons?

2. Linearly independent selectivity for shape and color in macaque inferotemporal cortex

2.1. Overview

The purpose of the experiment described in this chapter was to investigate how feature selectivity is integrated in inferotemporal cortex. Single neurons in IT are known to be sensitive to features of visual stimuli such as shape and color. Neural selectivity for stimulus features is widely believed to follow a nonlinear conjunction coding rule. According to this proposal, known as the "critical features" model, responses to an object that contains two of a neuron's preferred features will be greater than the sum of responses to both preferred features presented separately. An alternative possibility is that neural selectivity follows a linear coding rule. According to this model, a neuron's response to an object that contains two preferred features will be equal to the sum of responses to both preferred features presented separately.

In contrast, if IT neurons follow a linear coding rule, the sum of a neuron's responses to each feature presented separately should be equal to the response to an object that possesses both features. To determine which model better accounted for the properties of IT neurons, we recorded single unit responses to a set of stimuli in which two orthogonal features, shape and color, were manipulated independently. In the majority of IT neurons, selectivity for both features was integrated by linear summation. Only a small number of cells acted as nonlinear conjunction detectors. Accordingly, the feature conjunction hypothesis needs to be reconsidered.

2.2. Background

2.2.1 Feature selectivity in IT neurons

As we noted in the General Introduction, object recognition depends on the construction of a neural representation of that image at a high level of abstraction. This representation must be sensitive to the inherent properties of the object being viewed, and invariant to incidental image features that are attributable to the conditions of viewing. Neurons in IT display selectivity for stimulus features such as shape, color, and texture (Desimone et al 1984, Tanaka et al 1991, Komatsu and Ideura 1993), and are invariant to incidental aspects imposed by viewing conditions, such as location, size (Gross et al 1972, Ito et al 1995), and angle of illumination (Vogels and Biederman 2002). The implication of these findings is that IT transforms the low-level, veridical representation of the visual scene in early visual areas into a high-level representation based on a different set of feature dimensions. In early visual areas such as the striate cortex, the dimensions of the feature coding scheme are determined by the spatial location and filtering properties of V1 neurons, and are comparatively simple to characterize. In IT, by contrast, the dimensions of the feature coding scheme are poorly understood. Although there has been considerable success in identifying stimulus properties to which IT responses are invariant (e.g. Gross et al 1972, Ito et al 1995, Sary et al 1993, Rollenhagen and Olson 2000), understanding the dimensions of feature space has proven extremely problematic. Indeed, even though the object selectivity of IT neurons was first characterized thirty-six years ago (Gross et al 1969), we still cannot go very far beyond the very general claim that IT neurons are selective

for shapes, colors, and textures (Desimone et al 1984, Tanaka et al 1991, Komatsu and Ideura 1993). Moreover, even in cases where some of the dimensions of feature selectivity have been identified for a given neuron, it is not known how selectivity for multiple features in the same object are integrated. The difficulty in characterizing the stimulus space of IT representations is illustrated by the account of the discovery of hand cells, recounted in the General Introduction (Gross et al 1972). One suspects that a large number of IT neurons that appear completely unresponsive to visual stimuli actually have very interesting properties that are only rarely discovered (e.g. Baker et al 2001).

2.2.2 Linear feature integration in early vision

In contrast to IT, a substantial portion of the variance of visual responses in V1 neurons can be accounted for in terms of a relatively simple model. Most models of selectivity in V1 depend on a framework involving three stages: (1) a stage of linear spatial filtering within the receptive field, which governs (2) a nonlinear activation function, which gives rise to (3) spike generation according to a Poisson process (Adelson and Bergen 1985). The stage of linear spatial filtering instantiates the *a priori* hypothesis that V1 neurons act as filters of stimulus energy presented at the neuron's preferred spatial frequency and orientation. The fact that this hypothesis has good predictive value, combined with the fact that simple cells in V1 are linearly responsive to luminance contrast patterns within their receptive fields, has made it possible to characterize selectivity in V1 in an extremely efficient and systematic manner. A routine approach to classifying V1 simple cells is known as reverse correlation. This approach involves presenting a rapid succession of image frames with a random arrangement of white and dark pixels. The pattern of white and dark pixels that precede the firing of an action potential constitutes evidence

of the neuron's receptive field structure. After collecting a sufficiently large sample of such evidence, it is often possible to reconstruct a neuron's receptive field by linearly summing the luminance at each pixel in frames that preceded a spike (Ringach et al 1997, Mazer et al 2002, Reid et al 1997). The receptive field inferred by reverse-correlation can then be used to predict the responses to other classes of visual stimuli. While this approach has provided an extremely useful tool for studying visual processing in V1, it does not account for much of the variance in V1 responses to images with complex structure, such as realistic natural scenes (Smyth et al 2003, Touryan et al 2005). This fact probably reflects a bias in the choice of white noise stimuli that consist of pixel grids. Prediction of responses to natural scenes is better when natural scenes are also used to infer the receptive field structure (Carandini et al 2005), in other words when the bias introduced by the choice of stimulus type is consistent between the predictive and predicted stimuli.

2.2.3 Challenges of characterizing feature dimensions in IT

The fact that V1 responses can be characterized relatively well by a simple linear model constitutes an important theoretical advance in our understanding of early visual processing. This fact also offers the pragmatic advantage of providing an efficient method for studying V1 cells in the laboratory. In contrast to the situation in V1, no method is currently available for exhaustively searching the possible feature space of IT neurons in a systematic manner. Ideally, such a method would search feature space in a manner that is efficient (i.e. likely to produce an interpretable result most of the time), unbiased (i.e. not critically dependent on unlikely assumptions), and comprehensive in scope (i.e., generalizes to a broad class of stimuli, such as line-drawings, grayscale images, three-dimensional objects, disparity-defined forms, faces, a

herring, etc). In practice, a trade-off exists among these goals, and therefore most investigators have settled for biased methods of limited scope in exchange for the prospect of being able to collect an adequate body of data in a reasonable amount of time.

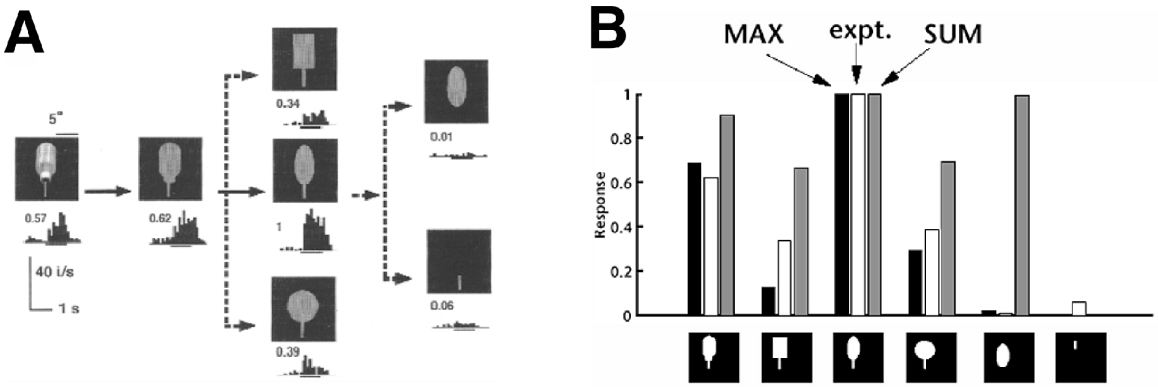


Figure 3. (A) Example of the stimulus reduction approach used to characterize the critical features of a neuron in anterior IT. This neuron was found to respond to a water bottle in a preliminary screening stage that included a large number of visual objects. The cell responded most strongly to a composite of two shapes, neither one of which was sufficient for driving the cell by itself. Accordingly, the critical features was identified by a conjunction of two shape components. **(B)** Results from a neural network modeling study comparing different rules of feature combination to the pattern of experimental data (white bars) shown in panel A. The model matched the experimental data better when it integrated features via a nonlinear (MAX) mechanism, rather than a by linear summation (SUM). Data originally derived from Wang et al (1998), reproduced in Riesenhuber and Poggio (1999).

In an early effort towards a systematic approach to feature characterization, Tanaka and colleagues pioneered an approach to identifying the principles underlying stimulus selectivity in IT (reviewed in Tanaka 1996). Their approach involved presenting a large set of objects in the receptive fields IT neurons, in order to identify an object that evoked a stronger response than any of the other items in the set (Tanaka et al 1991). Having found such an object, the final stage

was to construct two-dimensional images of that object in an effort to determine what features were necessary and sufficient to evoke highest observable response. Figure 3A shows an example of the initial effective stimulus for one such neuron, together with the image components that were ultimately identified as "critical features." Tanaka and colleagues used this feature reduction approach to assess how feature complexity becomes emphasized to a progressively greater degree at increasingly higher levels of the ventral processing pathway (Kobatake and Tanaka 1994). They focused particularly on anterior IT, and found that the majority of visually selective neurons were driven by complex shapes, or by some combination of shape with color or texture. The authors classified these neurons as "elaborate" cells, which they distinguished from "primary" cells that were maximally responsive to oriented bars or colored patches.

2.2.4 Conjunction coding models of object recognition

The work of Tanaka and colleagues has exerted a significant impact on ideas about the nature of object encoding in IT. Note that, in the example shown in figure 3A, the visual response evoked by the stimulus containing the necessary and sufficient "critical features" is greater than the sum of both image components (the ellipse and the bar) presented in isolation. In other words, this neuron responds specifically to a conjunction of two features, and the response to both critical features together cannot be predicted by observing the response to each component separately. Results from the feature reduction approach to characterizing selectivity in IT have been widely interpreted as indicating that IT neurons are feature conjunction detectors. A recent computational model of object recognition in IT has employed nonlinear feature summation explicitly as a mechanism for stimulus selectivity (Riesenhuber and Poggio, 1999). The

predictions of a model that instantiates a non-linear feature combination mechanism is compared to the results of both a linear model and Tanaka's experimental results in Figure 3B. The non-linear model corresponds more closely to the physiological responses of this neuron.

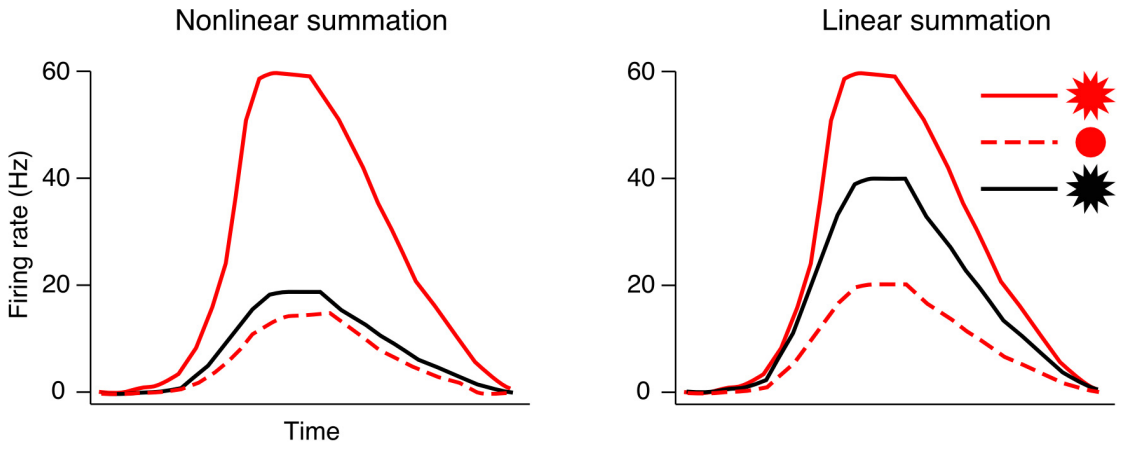


Figure 4. Schematic of two hypothetical IT neurons illustrating two alternative modes of feature integration. In both neurons, the maximal firing rate is evoked by a combination of two features, namely a star-shaped red object. The neuron in the left panel integrates the two features sub-linearly, in that the responses to objects that contain only one of the preferred features sum to less than the response to the red star. The neuron in the right panel integrates color and shape linearly, in that the sum of the responses to star-shaped objects and red objects predicts the response to the red star. Note that knowing the critical features for evoking the maximal response provides no information about the feature integration rule.

2.2.5 Critique and motivation

However, it cannot be concluded on the basis of results from feature reduction experiments (Tanaka et al 1991, Kobatake and Tanaka 1994) that IT neurons are conjunction detectors. According to the criteria used to identify the "critical features" for driving a cell, all features that were necessary for evoking the maximal were regarded as critical. This point is illustrated by the responses of two hypothetical neurons in Figure 4. The neuron in panel A is a true conjunction

coding neuron: its response to the two components together is greater than the sum of the responses to the two components presented in isolation. In contrast, the activity of the neuron in panel B is governed by linear summation: its response to the two components together is equal to the sum of responses to the isolated components. For both neurons, the feature reduction approach would identify the critical features of this neuron as a combination of shape (star) and color (red). Distinguishing between these two modes of feature integration requires an assessment of the neuron's responses to the sub-optimal stimuli.

Evaluating which feature integration scheme prevails in IT is problematic in the case shape feature combinations, because it is not generally the case that local features of complex visual stimuli can be manipulated independently. When shape components are added or removed from an object, incidental features other than those under investigation can also emerge (or be eliminated). For example, the "lollipop" composite stimulus in Figure 3A contains two acute L-shaped junctions located at the neck between the ellipse and the bar. The acute L-junctions are not present when either component shape is shown separately. In order to avoid this unintended nonlinearity of feature components at the level of the image, it would be necessary to employ a stimulus set in which shape components that are spatially separated from each other and therefore do not have overlapping edges (Baker et al 2002). This aspect of local shape features makes it difficult to assess the linearity of feature coding in IT for a general class of shape stimuli. For this reason, testing whether feature summation in IT follows a linear rule or a conjunction coding rule, it is convenient to manipulate feature dimensions that are truly orthogonal. Shape and color are orthogonal stimulus properties, in that one feature can be changed without affecting the other. In the experiment described in this section, we exploited

the orthogonal relation between shape and color in order to test the conjunction coding hypothesis. We asked whether responses to both shape and color dimensions could be accounted for by a linear model, or alternatively whether a nonlinear model was necessary.

2.3. Methods

Recording locations.

The recording locations were in anterior IT in the right hemisphere of two monkeys (CA and EG). Recording chambers in both monkeys were centered at Horsley-Clarke coordinates (18 anterior and 18 lateral). Physiological recordings were obtained primarily from the ventral convexity of area TE near the perirhinal sulcus, and in the lower bank of the superior temporal sulcus.

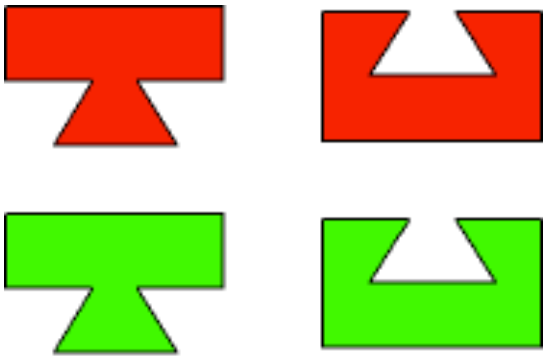


Figure 5. Example of a 2 x 2 matrix of stimuli employed in this experiment. Selectivity of each neuron was assessed using a counter-balanced matrix containing two shapes (tenon and mortise) and two colors (red and green).

Task and stimulus design.

Stimuli were selected from a library of 18 images that consisted of 9 pairs of mortise and tenon shapes, each of which fit within a 2.5 x 2.5 degree square . Each tenon stimulus all had a convex

feature on one side, and the corresponding mortise stimulus had a complementary interlocking concavity on one edge. These shapes were designed as components of a visual display, the figure-ground status of which was ambiguous and could be biased by contextual cues. For this reason both mortise and tenon stimuli appeared simultaneously on some trials. This aspect of the design is not of interest to the topic of this chapter, and will not be described further. For each experimental session, a 2 by 2 matrix of images was employed, the elements of which consisted of a mortise and tenon shape pair, each one of which could be either red or green. An example of one stimulus matrix used in this experiment is shown in Figure 5. The monkey initiated each trial by fixating on a central white dot, and was required to maintain fixation within an 3 degree window for the duration of the trial. Each item in the set was presented for at least 16 trials per stimulus.

Data analysis.

We quantified the firing rate evoked by visual stimuli by counting spikes within a time window of 80-400 msec following stimulus onset. To assess whether neurons were visually responsive, we conducted a paired, one-sampled t-test comparing the evoked visual response to the baseline firing rate obtained during fixation. Neurons were excluded from further analysis if they failed to display a significant positive visual response at a threshold of $p < 0.05$. To assess the pattern of stimulus selectivity of each neuron, we conducted a 2-factor ANOVA that modeled the effects of stimulus shape and color. On the basis of the significant main effects revealed by this ANOVA, neurons were classified as shape cells or color cells. To assess whether selectivity for shape and selectivity for color (as reflected by ANOVA main effects) were distributed independently in the population, we conducted a chi-squared analysis that compared the

expected and observed frequency of neurons with either two main effects or zero main effects. Firing rate histograms were constructed for both single neurons and for the population by summating the spikes across trials, and then convolving the mean instantaneous firing rate with a 10 ms Gaussian kernel.

2.4. Results

2.4.1 Single neuron results: independent summation of feature selectivity

We recorded from 139 neurons, of which 116 were visually responsive (69 in monkey CA, 47 in monkey EG). To assess the degree to which each neuron was selective for shape and color, we obtained the spike-count within a 80 to 400 msec window following stimulus onset. We collected visual responses from objects that were members of a 2x2 matrix, in which both shapes (mortise or tenon) and both colors (red or green) were counter-balanced (Figure 5). We then conducted a 2-level ANOVA that modeled the effects of the factors **shape** and **color** on the visual responses of each neuron. We observed several different patterns of selectivity. An example of a neuron that displayed one significant main effect for shape ($p = 2 \cdot 10^{-16}$) is shown in Figure 6. This neuron corresponds to the "cue-invariant shape selective" neurons that have been previously reported in IT, and it is what people primarily have in mind when they model how IT mediates object recognition. Figure 7 shows an example of a neuron with one significant main effect of color ($p = \sim 0$), with no sensitivity to shape. Such neurons have been described previously, and were reported to be as common as shape selective neurons (Komatsu et al 1992, Komatsu and Ideura 1993). Both of these types of neurons are consistent with the conjunction

coding framework that was proposed by Tanaka and colleagues (Tanaka 1996) and subsequently implemented in a computational framework by others (Riesenhuber and Poggio 1999). The critical question is, insofar as neurons are sensitive to both shape and color simultaneously, how is the neuron's selectivity combined? In the neuron shown in Figure 8, selectivity for the two dimensions summed linearly. This neuron had significant main effects for both shape and color ($p_{shape} = 10^{-5}$, $p_{color} = 10^{-7}$), but no interaction effect ($p_{int} = 0.55$). In other words, the neuron's selectivity for both stimulus dimensions is well accounted for by a linear model. This finding is contrary to the predictions of the trigger feature hypothesis, which posits that IT neurons detect conjunctions of their preferred stimulus attributes (Tanaka et al 1991, Riesenhuber and Poggio 1999). We also observed neuron's that conformed to the expectation of the trigger feature hypothesis, one example of which is shown in Figure 9. This neuron had a significant interaction effect ($p_{int} = 4 \cdot 10^{-8}$), although it also had significant main effects for both shape ($p_{shape} = \sim 0$) and color ($p_{color} = 2 \cdot 10^{-12}$).

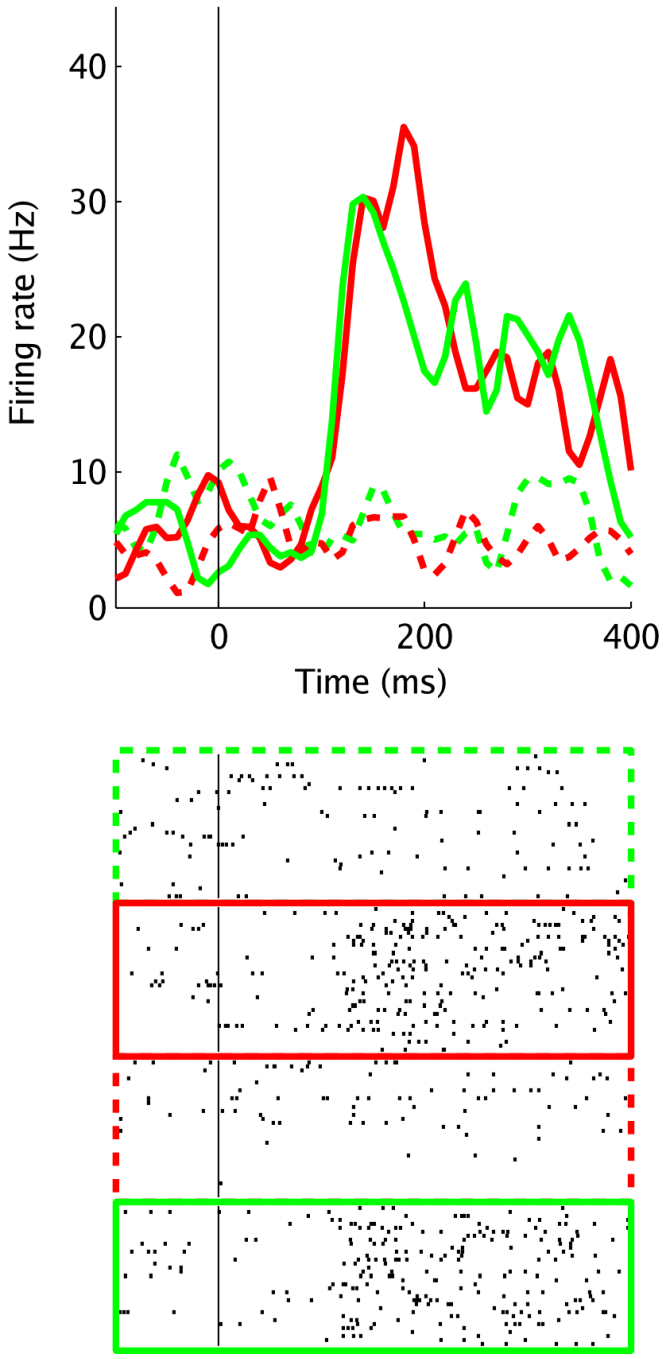


Figure 6. A single IT neuron from monkey EG with significant selectivity for shape ($p = 2x10^{-16}$, 2-way ANOVA) irrespective of color ($p = 0.96$). Top panel shows the firing rate histograms in response to four stimuli that comprised a 2 x 2 matrix. Tenon and mortise shapes are indicated by solid and dotted lines, respectively. The red and green lines correspond the stimulus colors. Bottom panels show raster plots for each of the four stimuli.

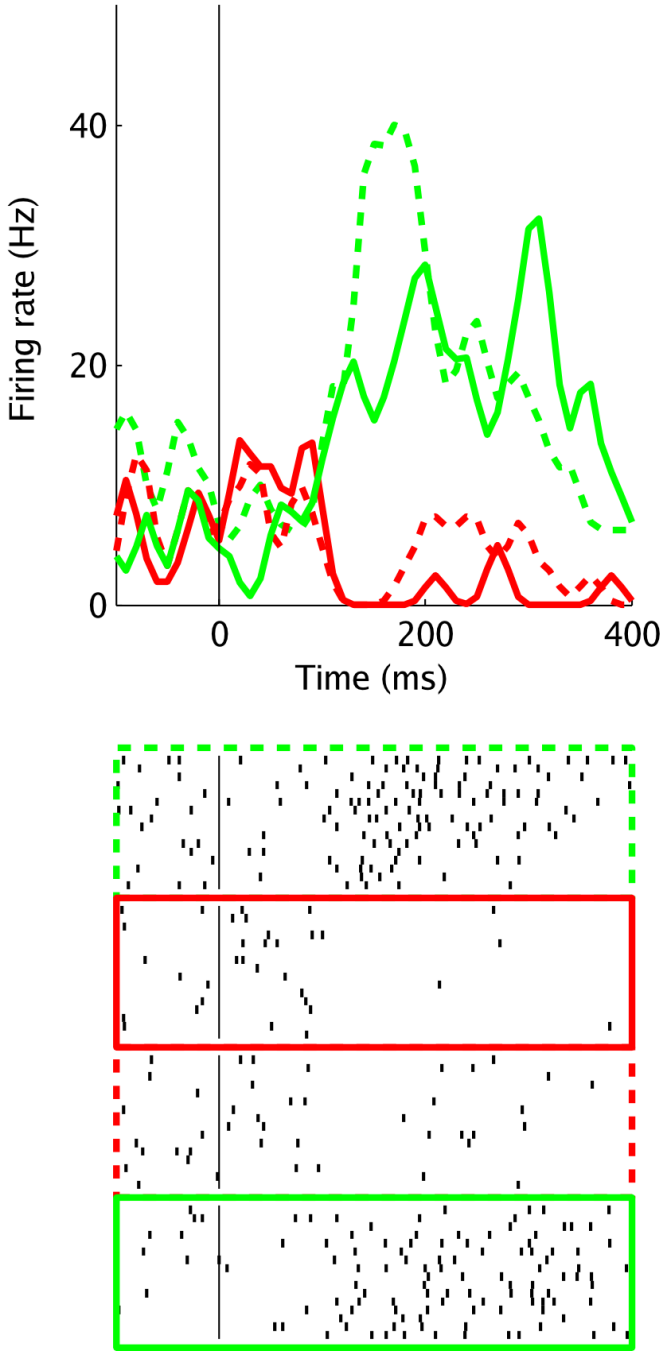


Figure 7. A single IT neuron from monkey CA with significant selectivity for color (p = 0) irrespective of shape (p = 0.43). Graphic conventions are as in Figure 6.

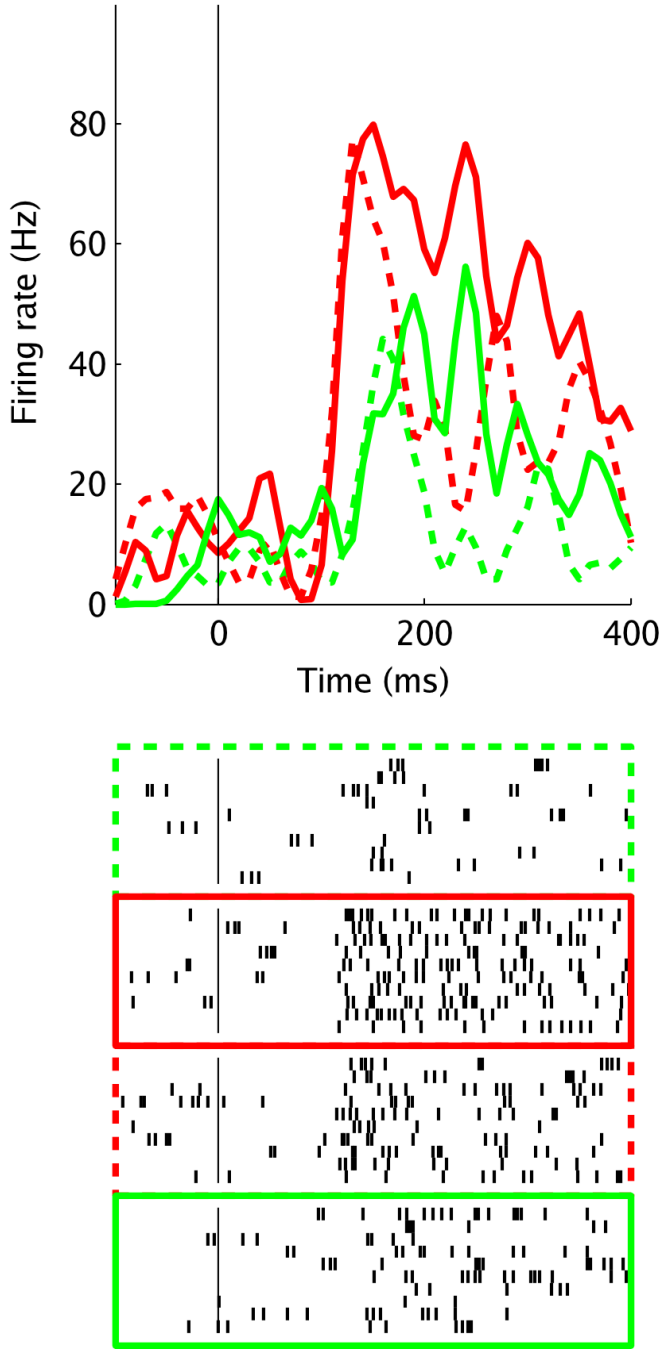


Figure 8. A single IT neuron from monkey CA with significant selectivity for both shape ($p = 10^{-4}$) and color ($p = 10^{-7}$). The absence of an interaction effect ($p = 0.55$) indicates that selectivity for both dimensions are integrated through linear summation. Graphic conventions as in Figure 6.

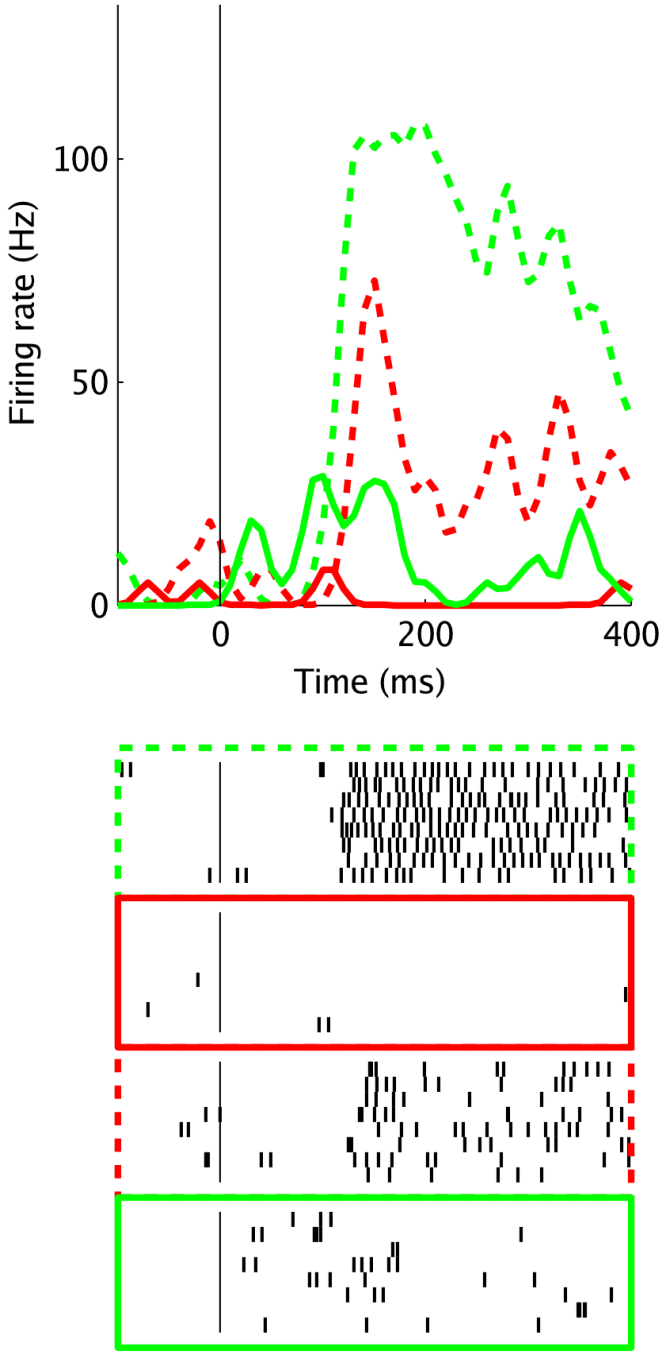


Figure 9. A single IT neuron from monkey CA with significant interaction effect ($p = 10^{-8}$), indicating selectivity for conjunctions of shape (mortise) and color (green). Neurons that responded to feature conjunctions were uncommon in our population, and when observed were frequently accompanied by main effects for shape or color. This neuron also had main effects of both shape and color factors. Graphic conventions as in Figure 6.

2.4.2 Population results: independent distribution of feature selectivity

Examples of neurons sensitive to feature conjunctions were rare. At the level of our sample population, the selectivity of most neurons was accounted for by a linear model. The white bars in Figure 10 show the distribution of main effects over the population. Interaction effects are indicated by the black bars. Out of all visually responsive neurons, 72% (92 out of 116) had at least one significant main effect. In contrast, only 14% of neurons (16 out of 116) had a significant interaction effect. The incidence of interaction effects was significantly greater than the expected number of type I errors ($p < 10^{-4}$, chi-squared test). In addition to being less common, interaction effects when present were less pronounced than linear effects. The distribution of F-statistics among neurons with main effects of shape and color (medians 17.4 and 14.4, respectively) were greater than the F-statistic distribution among interaction neurons (median = 7.1; $p = 0.03$, Wilcoxon rank-sum test). Thus, although a small number of neurons in IT combine selectivity for shape and color dimensions in a nonlinear manner, these conjunction coding effects are substantially weaker than linear effects.

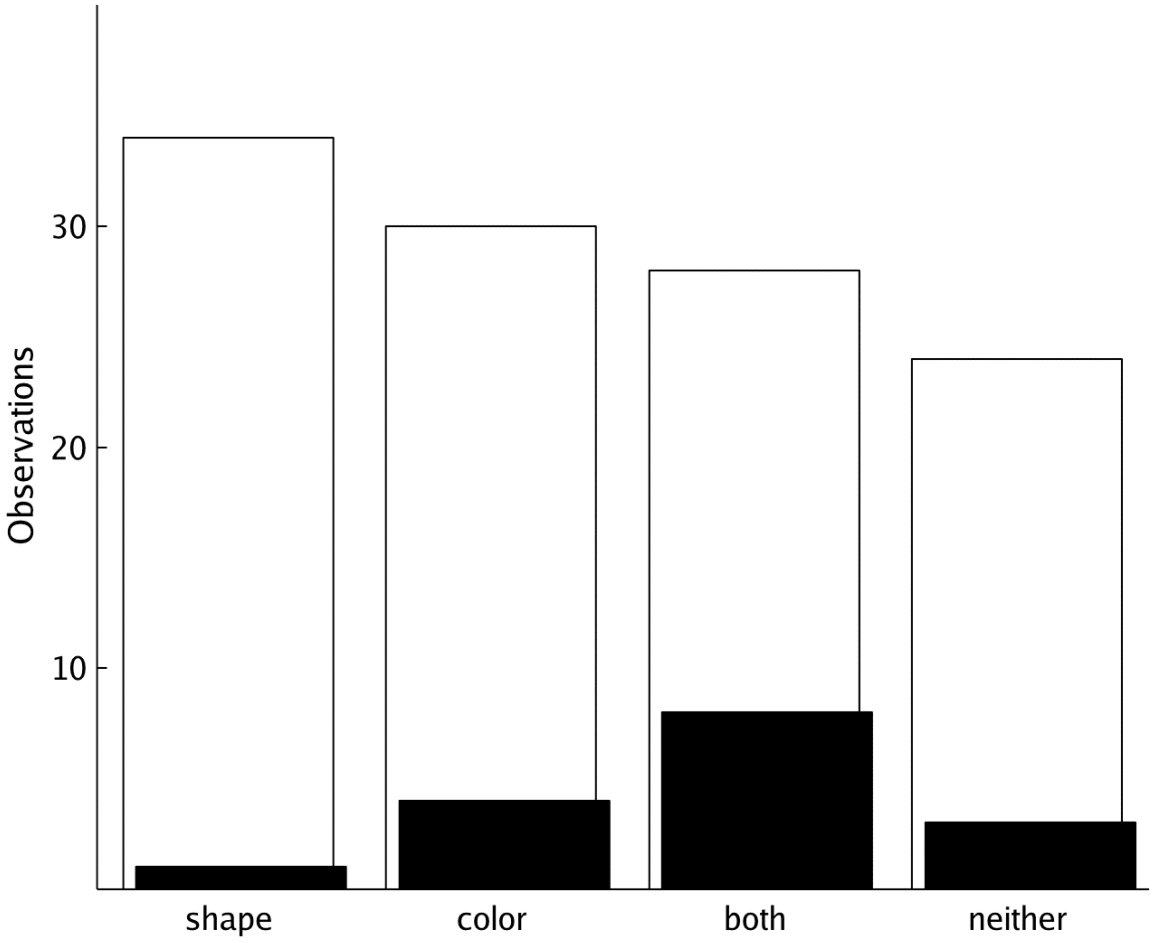


Figure 10. Distribution of feature selectivity effects for the population of visually responsive neurons (N = 116). Feature selectivity was assessed by a 2-factor ANOVA. Height of the white bars indicates the number of neurons that displayed either one main effect of shape, one main effect of color, main effects for both features, or no main effects. Neurons in the last category responded to visual stimuli but did not distinguish among them. Height of the black bars indicates the incidence of significant interaction effects among the classes of linear coding effects described above.

These results indicate that, for most neurons, selectivity for color and shape contribute independently to a neuron's visual response. We next asked whether selectivity for both stimulus dimensions occurred independently at the level of the population. Table 1 summarizes the incidence of main effects across the population. The incidences of main effects of shape and color were 53% and 50% respectively. Out of all 116 neurons, 24% had main effects for both shape and color, which is not significantly different from what would be expected if selectivity for both shape and color were distributed independently across the entire population ($p = 0.43$, chi-squared test). We observed this independence in the population of neurons from monkeys considered separately, despite the higher incidence of color selective cells in monkey CA, and the opposite trend in monkey EG. This finding is consistent with the results of a previous study of color selectivity at the population level (Komatsu and Ideura 1993). Thus, knowing whether or not a neuron is selective for shape provides no information as to whether or not that same neuron is also selective for color.

Population distribution of feature selectivity

	shape	**color**	**interaction**	**total**
monkey CA	28	44	12	69
monkey EG	34	14	4	47
total	62	58	16	116

Table 1. Observations of shape and color cells and interaction cells over the population of neurons recorded in both monkeys. Shape and color main effects were distributed independently at the level of the population, in that knowing whether a neuron was shape selective provided no information about whether the same neuron was also color selective ($p = 0.43$, chi-squared test).

2.5. Discussion

In this chapter, we tested the hypothesis that IT neurons are conjunction detectors. The conjunction coding hypothesis predicts that selectivity for orthogonal feature dimensions such as shape and color will be integrated in a supralinear manner. We rejected this hypothesis for the majority of IT neurons. Instead, we found that a linear model is sufficient to account for the selectivity for the majority of IT neurons. Moreover, in the rare instances of significant interaction effects, the increase in explanatory power gained by including the nonlinear effect was comparatively small. In light of these findings, the conjunction coding hypothesis needs to be reassessed.

As noted in the section 2.2, the general findings of Tanaka et al (1991) could be accounted for in terms of either a conjunction coding model or a linear model, at least as far as integration of the orthogonal dimensions of shape and color are concerned. We did not assess whether the same finding applies to integration of shape features. Nonetheless, our findings are also consistent with more recent studies of selectivity for shape components in IT. Brincat and Conner (2004) found that, when the shapes are parametrically varied over a very large stimulus set, most IT neurons respond to the stimuli in a way that can be accounted for in terms of linear summation of the feature components independently. The results of this study reflect a surprising degree of linearity, considering that the parametric manipulations they employed were not specifically designed to prevent shape components with nearby edges from producing incidental features.

Close proximity of shape components can result in inadvertent feature creation or deletion when components are changed.

Baker et al (2002) conducted an experiment using stimuli that were designed so that the components could be changed without interfering with each other, as the components were spatially separated within the object. In this study, training the monkeys to respond differently to the stimuli on the basis of feature conjunctions significantly increased the prevalence of nonlinear conjunction detectors (from 9% for untrained objects to 18% for trained objects). Thus, nonlinear integration becomes more common if a specific conjunction of two features is behaviorally relevant. This finding suggest that IT employs two feature integration strategies simultaneously. A large pool of neurons integrates stimulus features by using a linear mechanism. This representational strategy is computationally simple, and can accommodate a wide range of visual objects that might be encountered. Thus, linear coding might be more generally useful for representing information in an unpredictable sensory environment. In contrast, a smaller pool of neurons integrates stimulus features by using a conjunction coding mechanism. This representational strategy is more limited in scope, since each neuron would only respond to a very restricted class of stimuli. Thus, conjunction coding might be reserved for visual objects that are encountered frequently, or are especially important to behavior.

How important are shape-color conjunctions for object recognition? Color cues can serve to constrain the interpretation of objects in the visual world in a manner that goes beyond the role of color in defining object boundaries. Results from computer vision studies indicate that color information provides a useful cue to object identity when shape information is not available

(Swain and Ballard 1991, Mel 1997). Moreover, although color and shape processing channels are both sufficient for recognizing intact objects when information from the other modality is not available, object recognition in computer vision is more robust to stimulus degradation if both shape and color information is available (Mel 1997). However, in normal human subjects, color does not seem to be used as a salient cue for object recognition when unambiguous shape information is available, even in the case of objects for which color information is potentially diagnostic, such as a banana or an orange (Biederman and Ju 1988, Aginsky and Tarr 2000). Moreover, object recognition is spared in achromatopsia patients, in whom color perception is abolished (Zeki 1993), and color is generally not helpful in the case of patients with agnosia (Mapelli and Behrmann 1997). These findings indicate that color perception is not necessary for object recognition when the interpretation of shape is sufficiently constrained by information from other visual cues.

Summary and Conclusions.

In this chapter, we showed that selectivity for two orthogonal feature dimensions - shape and color - are integrated in inferotemporal cortex according to a linear model. For most single neurons in IT, responses to conjunctions of shape and color could be predicted on the basis of the neural response of the two features when presented separately. Across the population of IT neurons, selectivity for both shape and color was distributed independently, in that knowing whether a neuron was selective for shape provided no information as to whether the neuron was also selective for color. A minority of neurons were found to respond nonlinearly to conjunctions of shape and color. These results indicate that objects are represented by a set of

linearly independent distributions of activity across the population of neurons in IT. This arrangement may serve to encode visual features in a simple, flexible, and efficient manner.

3. Neural activity accompanying repetition priming in macaque inferotemporal cortex

3.1. Overview

The experiment described in this chapter focuses on the relation between behavioral priming and neuronal suppression. Both phenomena are induced by repeated presentations of visual stimuli, but it is not known whether the two are related. In the background section, we examine the current state of our knowledge of priming and its possible neural correlates. Specifically, we will review what is currently known about the effects of stimulus repetition at the levels of behavior, single unit physiology, and functional imaging. We will then assess the evidence pointing to a relation among these phenomena. In the results section, we present evidence that repetition priming and repetition suppression are induced by the same conditions. We assess the effect of stimulus repetition on stimulus selectivity by comparing our physiological data to the predictions of two models that seek to account for how repetition suppression varies as a function of stimulus efficacy. We conclude with discussion of our new experimental findings in the context of previous and future studies of object recognition.

3.2. Background

In this section, we present the background that motivates this experiment. In part 1, we will consider the behavioral effects of stimulus repetition that have been observed in human subjects. In parts 2 and 3, we will review the effects of prior stimulus exposure on neuron in early visual cortex and in IT, respectively. Part 4 addresses functional MRI experiments that investigate the effects of stimulus repetition on brain activity in humans. Part 5 describes the extent to which MRI evidence serves to bridge the gap between behavioral priming effects observed in humans and cellular effects of stimulus repetition observed in monkeys. We conclude in part 6 with a statement of experimental aims designed to address the areas where our understanding is lacking.

3.2.1 Behavioral priming in humans

What is repetition priming?

Repetition priming is a form of implicit memory, whereby prior exposure to a stimulus allows faster or more accurate processing of that stimulus on subsequent exposures (Tulving and Schacter 1990, Schacter and Buckner 1998). Priming is an extremely rapid form of perceptual learning, and can often be induced by a single presentation of a visual stimulus. The magnitude of priming effects diminishes over increasing intervals between the initial and subsequent presentations of a stimulus (referred to as the "prime" and "probe" stimulus presentations; e.g. Scarborough et al 1997, Kersteen-Tucker 1991, McKone 1995a). Nevertheless, some residual

effect of priming often persists over long intervals. The temporal persistence of priming, in addition to its insensitivity to visual material intervening between prime and probe stimuli (McKone 1995b), is sufficiently reliable to allow for presentation of several prime and probe items in separate blocks (referred to as "study" and "test" blocks; e.g., Biederman and Cooper, Srinivas 1995, Cave 1997). Indeed, residual priming in picture naming tasks has been demonstrated to persist over several days (Mitchell and Brown 1998), weeks (Cave and Squire 1992), and even as long as one year (Cave 1997). Although only a single repetition is necessary to induce priming, the magnitude of priming is generally cumulative over multiple stimulus presentations (Brown et al 1996, Wiggs et al 1997, Buckner et al 1998). These findings indicate that the visual system is exquisitely sensitive to repeated exposure to a given stimulus, and that this sensitivity has significant behavioral consequences.

Perceptual priming is distinct from semantic priming.

A key principle that has emerged in the study of implicit memory is the distinction between perceptual and semantic priming effects. In semantic priming, repetition effects are due to a commonality between the meaning or significance of prime and probe. Such repetition effects tend to be very short lived, decaying over a few seconds (Graf et al 1985). These effects presumably depend on activity propagation within a network of semantic associations at the level of category membership, as opposed to image structure. In contrast, repetition effects observed in perceptual priming studies are attributable to structural similarity between the visual images presented at prime and probe (Biederman and Cooper 1992, Cooper and Schacter 1992, Srinivas 1996). This form of priming is the focus of this chapter. Although perceptual priming is thought to be a phenomenon distinct from semantic priming or explicit memory, it is rarely the case that

perceptual priming can be studied in isolation. Perceptual decisions generally result in some degree of contamination by semantic association or explicit memory. Mixed semantic and perceptual effects will be particularly pronounced if the response required of the subjects in priming tasks is inherently semantic in its processing demands (e.g., lexical decision, picture naming, picture categorizing).

Priming is distinct from explicit memory.

An extensive body of research (reviewed in Schacter et al 1993, Schacter and Buckner 1998, Henson 2003) indicates that repetition priming is functionally distinct from explicit memory. Four lines of evidence support this conclusion. First, neuropsychological studies indicate that human patients with medial temporal lobe lesions that suffer from severe deficits in explicit recall can display relatively normal implicit priming effects (Warrington and Weiskrantz 1968, Cave and Squire 1992). Conversely, damage to extrastriate visual areas, which do not affect explicit memory, can result in impaired implicit priming (Gabrieli et al 1995). Second, explicit memory is facilitated when human subjects perform tasks that require a greater depth of processing. By contrast, priming is relatively unaffected by such manipulations (Mandler et al 1986). Third, perceptual priming effects are sensitive to manipulations of the image form of a visual stimulus that do not affect meaning (such as changing type-font between prime and probe; Graf and Ryan 1990). Semantic priming effects, however are insensitive to such manipulations. Fourth, the expression of repetition priming and explicit memory are stochastically independent, in that prior exposure to a stimulus primes subsequent exposure, regardless of whether the subject is consciously aware that the stimulus has been repeated (Jacoby and Witherspoon 1982).

These converging lines of evidence establish that repetition priming represents a form of implicit memory, whereby learning can proceed without explicit awareness.

Priming as a methodological tool.

A great deal of the interest in priming in recent years is due not only to the phenomenon in its own right, but also as a means of using behavioral measures to indirectly probe the structure of neural representations. The logic of this approach is as follows: first, visual images are presented during a study phase. Second, in the test phase, behavioral responses are collected to stimuli that are different in some way from the images presented in the study phase. If behavioral priming is robust to the stimulus transformation, the interpretation is that both versions of the stimulus are represented by a common population of neurons. Conversely, if priming is disrupted by the transformation, the interpretation is that the images presented during the study and test phases are represented by distinct population of neurons. Several studies have used this approach to demonstrate that priming is insensitive to image size (Biederman and Cooper 1992, Cooper and Schacter 1992, Srinivas 1996), translation (Biederman and Cooper, Bar and Biederman 1999), and lateral mirror image reflection (Cooper and Schacter 1992, Srinivas 1996). In contrast, priming is abolished by depth rotation (Srinivas 1995), or by differences in type font in the case of word strings (Graf and Ryan 1990, Jacoby and Hayman 1987, Wiggs and Martin 1994). This approach has also been used to shed light on the processing level at which priming is likely occur. Bar and Biederman (1999) demonstrated that priming in a masked-stimulation paradigm is abolished by changes in stimulus location from one quadrant of the visual field to another. On the basis of this finding, they argued that masked priming effects must be mediated by neurons with receptive field sizes that match the spatial extent of translation invariance. Such neurons

are commonly found in posterior IT. This finding is in general agreement with neuropsychological studies that showed that lesions to ventral visual areas disrupt priming effects (Gabrieli et al 1995, Walsh et al 2000). The study of priming effects is also prominent in the ongoing debate about whether neural representations of form are expressed relative to a viewer-centered or object-centered reference frame. This debate has been waged in large part on the basis of whether or not priming effects are viewpoint invariant (Tarr et al 1998, Biederman and Bar 1999).

What neural mechanisms underlie priming?

Given the extensive use of behavioral priming measures to infer the properties of neural representations, it is clearly of interest to understand the cellular mechanisms that mediate priming. Because early psychological accounts of priming mechanisms were formulated at a relatively high level of abstraction, it is not straightforward to derive predictions from them that are biologically plausible and readily testable (see Schacter and Buckner 1998 and Henson 2003 for reviews). "Spreading activation" theories accounted for priming in terms of residual activity within the systems mediating perception (Neely 1977). Insofar as such accounts predict persistent firing in individual neurons, they clearly cannot account for long-lasting priming effects, although it is likely that such accounts could explain priming over very short intervals (e.g., Behrmann and Kimchi 2003). In contrast, connectionist theories of priming have been more promising, in that they are based on a biologically plausible computational framework. A recent neural network model proposed that repetition priming effects are due to potentiation of connections between units encoding a visual stimulus as a result of multiple exposures (Stark and McClelland 2000). This model predicts that behavioral priming should be accompanied by

increases in neural activity. However, as we shall review in detail in section 2.1.4, behavioral priming in humans is commonly accompanied by decreases in brain activation rather than increases (Buckner et al 1998). This observation has been widely replicated, and therefore theoretical accounts of priming must account for this paradoxical finding. One widely held theory is that reductions in brain activity are a result of repetition-induced sharpening of stimulus selectivity at the level of single neurons in visual cortex (Desimone 1996, Wiggs and Martin 1998). In later sections, we will consider the evidence from physiological and imaging studies that constrain the possible biological mechanisms that could contribute to priming. Subsequently, we present results from a priming experiment in monkeys designed to test the sharpening hypothesis explicitly.

3.2.2 Physiological effects of stimulus repetition: early visual cortex

Contrast adaptation in V1.

Prior exposure to visual stimuli has a profound impact on neural activity in the early visual system. Contrast adaptation, defined as visual response decreases following exposure to stimuli with structured patterns of luminance contrast such as sinusoidal gratings, has several properties that make it a convenient model system for studying such effects. Most notably, contrast adaptation to grating patterns is orientation specific, and has been shown to originate within V1. Intracellular recordings in the striate cortex of anesthetized cats have established that a prolonged after-hyperpolarization mediates contrast adaptation to grating patterns presented over sustained intervals of at least 20 seconds (Carandini and Ferster 1997, Sanchez-Vives et al 2000a). *In vitro* recordings from ferret visual cortex neurons establish that this after-hyperpolarization current is mediated by K^+ currents and is sensitive to intracellular [CA^{++}]. The fact that this

hyperpolarization can be induced by direct intracellular current injection, as well as in response to visual stimulation, indicates that it is due to intrinsic membrane properties of V1 neurons (Sanchez-Vives et al 2000b). However, it is not clear that contrast adaptation effects induced by such prolonged conditioning exposures are commonly of behavioral relevance. Contrast adaptation effects are inducible by brief (500 ms) stimulus exposures in V1 neurons of anesthetized macaques (Muller et al 1999). Adaptation induced in this paradigm recovered with a time-constant of 6 seconds. Interestingly, contrast adaptation to brief grating patterns is orientation specific for complex cells, but not simple cells (Muller et al 1999). The effect of contrast adaptation on orientation selectivity in complex cells is to shift the cell's tuning curve away from the adapting stimulus. Fixation intervals on the order of hundreds of milliseconds occur regularly in the course of active vision, thus contrast adaptation is likely to be induced under behaviorally relevant circumstances (Dragoi et al 2002).

Motion adaptation in MT.

A particularly striking consequence of prior exposure can be demonstrated by observing visual motion over a prolonged interval. This prolonged exposure results in an optical illusion known as the motion aftereffect or the "waterfall" effect (Mather 1998). The consequence of this illusion is that subjective perception of motion is biased in the opposite direction of the conditioning motion stimulus. For example, prolonged exposure to downward motion causes a subsequent stationary stimulus to be perceived as moving upward. The neural correlates of visual motion have been studied extensively in the middle temporal area (MT), a motion sensitive region in the dorsal processing pathway that receives a strong direct projection from V1. Motion adaptation is stimulus specific, in that visual response suppression is maximal when

the motion presented as both conditioning and test stimuli is in the same direction. In a manner analogous to contrast adaptation in V1 complex cells (Muller et al 1999), motion adaptation in MT shifts the direction tuning curve away from the direction of the adapting stimulus (Kohn and Movshon 2004). Motion adaptation has typically been studied with conditioning stimuli presented for relatively long durations, on the order of 20 seconds. Under such circumstances, adaptation is inherited from contrast adaptation among V1 neurons (Kohn and Movshon 2003). However, when conditioning stimuli are presented for intervals on the order of hundreds of milliseconds, adaptation is attributable to mechanisms arising within MT (Priebe et al 2002). Adaptation induced on behaviorally relevant time-scales results in a reduction in perceived speed accompanied by an improvement in speed discrimination (Krekelberg et al 2005). This suggests that adaptation is a beneficial process that facilitates visual perception, rather than an incidental consequence of neuronal fatigue.

3.2.3 Physiological effects of stimulus repetition: inferotemporal cortex

Stimulus repetition induces neuronal suppression in IT.

Several studies have described firing rate reductions in IT resulting from repeated stimulus exposures. This phenomenon is referred to as "repetition suppression" (Desimone 1996), and has been observed under a wide range of circumstances. The properties of firing rate suppression are highly sensitive to cognitive task requirements, as well as to the time-interval separating the initial and repeated stimulus presentations. The earliest demonstrations of repetition suppression in behaving monkeys employed a serial memory task, which requires the subject to remember each element in a sequentially presented set of objects (Baylis and Rolls 1987, Riches et al 1991, Fahy et al 1993, Sobotka and Ringo 1994). Under these circumstances,

firing rates in IT are higher in response to initial stimulus presentations than to subsequent exposures that occur in later trials. Considerably stronger suppression effects have been reported for within-trial stimulus repeats, over brief inter-stimulus intervals ranging from 300 ms to 1500 ms (Baylis and Rolls 1987, Fahy et al 1993, Sobotka and Ringo 1993, Sary et al 1993). Some investigators have reported that neurons which undergo strong within-trial response suppression over short time spans are the same neurons that undergo the strongest suppression over longer, across-trial intervals (Li et al 1993, Sobotka and Ringo 1993). This finding has lead to the proposal that the observed firing rate reductions both within and across trials reflect that same underlying phenomenon (Sobotka and Ringo 1993, Desimone 1996). However, such an interpretation requires that a single biological mechanism mediate suppression over time intervals spanning two-orders of magnitude (e.g. from 300 ms to 30 sec). Since it is not clear that a single cellular mechanism does in fact span the appropriate time scale, the term "repetition suppression" will be used in this thesis to refer exclusively to firing rate reductions observed for inter-stimulus intervals on the order of seconds.

Repetition suppression is automatic.

The fact that repetition suppression was first observed in the context of serial recognition tasks initially led to the suggestion that repetition suppression played a role in explicit memory. However, stimulus repetition and explicit recall are typically confounded in most recognition memory tasks, thus it was unclear which factor contributed to neuronal suppression. To dissociate these two factors, Miller and Desimone trained monkeys to perform a variant of the delayed-match to sample task, which they referred to as the "ABBA" task. In this task, subjects are required to respond explicitly to a "probe" image that matched a previously presented

"sample" image, while ignoring repeated non-matching probe stimuli (Miller and Desimone 1994). Under these circumstances, repetition suppression was observed for repeated non-matching probe stimuli. In contrast, visual responses to matching probes were actually increased in some neurons, which the authors described as "match enhancement". The opposite effect ("match suppression") was observed in the remaining neurons that distinguished between the sample and the matching probe. These observations imply that repetition suppression is not strongly linked to explicit memory processes. This proposition is further supported by three additional lines of evidence. First, over brief intervals of several hundred milliseconds, stimulus repetition occurs regardless of whether the subject is passively fixating or is required to respond to identical repeats (Sary et al 1995). Second, passive fixation is also sufficient to induce repetition suppression over longer intervals ranging from 2 to 6 seconds (Miller et al 1991). Finally, the fact that repetition suppression persists over multiple intervening stimuli when the animal is not required to remember the repeated stimulus across trials establishes that explicit memory is not necessary to induce repetition suppression in IT neurons (Li et al 1993, Fahy et al 1993). Accordingly, repetition suppression appears to reflect an automatic process that does not depend on the maintenance of an image in working memory.

How long does repetition suppression persist?

There is some discrepancy as to the persistence of repetition suppression effects. Some groups have reported that suppression is abolished by the presentation of one, or at most two intervening stimuli (Baylis and Rolls 1987, Sobotka and Ringo 1994). However, suppression effects have also been demonstrated after multiple intervening trials (Li et al 1993), and one study employing chronically implanted recording electrodes reported suppression effects persisting as long as 24

hours (Fahy et al 1993). The discrepancy may simply reflect functional heterogeneity among recording sites within IT (Fahy et al 1993, Xiang and Brown 1998). Another possible explanation is that tasks requiring explicit memory might actively interfere with repetition suppression (Li et al 1993, Fahy et al 1993). In light of the match enhancement effects observed in the ABBA task (Miller and Desimone 1994), the brevity of repetition suppression observed in some explicit memory tasks (Baylis and Rolls 1987, Sobotka and Ringo 1994) might arise from the combined effect of repetition suppression and match enhancement. Differences in the persistence of repetition suppression across studies may also reflect the confounding influence of stimulus novelty.

Effect of stimulus novelty on repetition suppression.

Neural activity in IT is influenced by whether visual stimuli are either novel or familiar to the animal. Irrespective of repetition, visual responses to initial presentations of visual stimuli are considerably stronger for novel than for familiar stimuli (Fahy et al 1993, Li et al 1993, Xiang and Brown 1998). Moreover, novel stimuli also induce a stronger degree of suppression, in terms of absolute firing rate, upon repeated exposures (Fahy et al 1993, Li et al 1993). This finding has led to the suggestion that a class of IT neurons act as "novelty detectors," which serve to ensure that visual representations in IT are sensitive to changes in the visual environment (Xiang and Brown 1998). However, it is not the case that IT neurons respond indiscriminately to novel objects without regard to stimulus features. The difference between novel and familiar objects likely reflects the initial stages of visual learning mediated by long-term plasticity within visual cortex (Miyashita 1993). Another possibility is that novel stimuli evoke stronger visual responses than familiar stimuli because they are more effective at

capturing visual attention (Chelazzi et al 1993). This interpretation is, of course, not incompatible with an explanation based on long-term memory effects.

3.2.4 Functional imaging studies of stimulus repetition in humans

In the previous sections, we considered the effects of stimulus repetition on visual responses of single neurons in monkey visual cortex. In this section, we consider the effect of stimulus repetition on human brain activity observed in functional imaging studies. We will focus primarily on the lateral occipital complex (LO), which is the region in the human brain homologous IT (Malach et al 1995).

Effects of stimulus repetition on brain activation in humans.

A broad consensus has now emerged that stimulus repetition commonly induces a decrease in the level of brain activation evoked by visual stimuli. The earliest demonstration of this phenomenon was reported in a study by Squire et al (1992). In this study, the authors conducted a PET scan on subjects who were performing a word-stem completion task. The authors found that when the subjects were presented in the test phase with word stems that had previously been encountered during the study phase, there was a decrease in activation in ventral visual cortex. Subsequent fMRI studies have repeatedly established that stimulus repetition results in BOLD signal reductions in LO (Buckner et al 1998, Grill-Spector et al 1999, Jiang et al 2000, Eger et al 2004, Ishai et al 2004). Notably, this decrease in brain activity has not generally been observed in lower level visual cortex (Buckner et al 1998, Grill-Spector et al 1999, Avidan et al 2002, Fang et al 2005) which has been interpreted as reflecting an equivalence between repetition suppression in monkey IT and BOLD signal reductions in human LO but not in early visual

cortex. A recent imaging study has confirmed that stimulus repetitions induce reductions in cerebral blood flow are restricted to IT in awake fixating monkeys (Sawamura et al 2005).

Repetition-induced increases in activation can be explained by hysteresis in object recognition. The human brain imaging literature indicates that stimulus repetition most commonly leads to decreases in brain activity. There have, however, been several noteworthy exceptions. One such PET study investigated visual responses evoked by "Mooney faces," the features of which have been degraded by removal of grayscale contrast structure. Such stimuli are commonly unrecognizable as faces upon first viewing, but are readily recognized after the full grayscale images has been presented. The authors demonstrated that Mooney faces initially evoke visual weak responses, but the same images evoked strong responses once they had been rendered recognizable (Dolan et al 1997). Similar results have been obtained by manipulating the luminance of letter strings (Kleinschmidt et al 2002) or the chromatic polarity of face stimuli (George et al 1999), both of which render previously unrecognized stimuli recognizable. In all of these cases, the increase in brain activation occurred under circumstances in which the stimuli were unrecognizable on the initial exposure, and subsequently rendered recognizable through some manipulation between prime and probe. Accordingly, the lower activation evoked by initial stimulus presentation can be attributed to a failure to engage object recognition. In other words, increases in brain activity related to stimulus recognition reflect the inherent hysteresis of object recognition at the level of perception (George et al 1999, Avidan and Behrmann 2002). This explanation is further supported by imaging studies of stimulus masking, which involves abbreviating the duration of visual stimuli to the point where multiple exposures are necessary for recognition. Under such circumstances, activity in LO is correlated with successful stimulus

recognition (Grill-Spector et al 2000, Bar et al 2001, Schnyer et al 2002, James and Gauthier, in press).

Repetition of unfamiliar stimuli can induce activation increases.

However, not all cases of repetition-induced increases can be attributed to the hysteresis of object recognition. Several imaging studies have reported that, whereas repetitions of *familiar* stimuli result in the commonly observed decreases in brain activity, repetitions of *novel* stimuli result in increased visual responses. This effect has been induced by a broad range of visual images, including line drawings interpretable as 3-dimensional objects (Schacter et al 1995), hieroglyph-like icons (Henson et al 2000), and unfamiliar human faces (Henson et al 2000, Thiel et al 2002). In these studies the enhancement of brain activity could not be attributed to an improvement in recognition. In all cases, the novel items were recognizable upon initial presentation, even if they were not identifiable. For instance, although it is not possible for subjects to provide the name that goes with an image of an unfamiliar face, it is still possible to recognize the image as a face (Henson et al 2000). This aspect of the human imaging literature appears to directly contradict the findings from primate physiology that novel stimuli induce greater repetition suppression than familiar stimuli (Li et al 1993, Fahy et al 1993, Xiang and Brown 1998). This discrepancy remains to be resolved. Improvements in the spatial resolution of functional imaging may be able to clarify which distinct subregions within LO undergo BOLD signal enhancement, as opposed to suppression (e.g., George et al 1999, Vuilleumier et al 2002).

MR adaptation as a methodological tool.

Previously, we reviewed the use of behavioral priming effects to probe the structure of object representations in the human visual system. We then noted that stimulus repetition commonly induces reductions in brain activity in human visual region LO. In recent years, this MR adaptation effect has been exploited to draw inferences about the response properties of single neurons in visual cortex. This approach offers the possibility of circumventing the limited spatial resolution of MR signals, which is typically on the order of 1 mm^3. The general logic of this approach is as follows (Grill-Spector and Malach 2001). First, subjects view an adapting stimulus, typically multiple presentations of the same object. Second, BOLD responses are evoked by a test stimulus, which may differ in some respect from the adapting stimulus. The degree to which MR adaptation is maintained despite stimulus transformations indicates the degree to which individual neurons are driven by both the adapting stimulus and the test stimulus. This approach depends on the assumption that the strength of suppression is proportional to the strength of the visual response. This prediction was tested by assessing the effect of repeating low-contrast images on adaptation in LO (Avidan et al 2002). In this study, the authors showed that low contrast stimuli evoked weak initial responses in LO, and these responses undergo little or no adaptation upon repetition. By comparison, weak BOLD signal responses to marginally effective stimuli presented at full contrast were nonetheless capable of inducing strong adaptation effects. This pattern of results is consistent with the interpretation that MR adaptation is indeed proportional to the firing rate.

The MR adaptation method was first employed by Grill-Spector et al (1999), who assessed the effects of changes in stimulus location, size, and viewing angle on LO responses. Whereas MR

adaptation in LO was maintained despite changes in location and size, rotated versions of the same signal permitted a recovery from adaptation that was comparable to the effect of presenting an entirely new stimulus. These results are consistent with the properties of location and size invariance revealed by physiological recording studies in monkeys (Gross et al 1972, Ito et al 1995), and also consistent with the failure to observe viewpoint invariance to rotated stimuli (Logothetis et al 1995). The finding that adaptation in LO is size invariant has recently been confirmed independently (Sawamura et al 2005). Taken together, these observations support the general viability of using the MR adaptation approach to study the neural substrates of object representations in humans.

Several subsequent studies have revealed a number of interesting aspects of stimulus selectivity and invariance in LO. For example, reversing the figure-ground status of components in a display with ambiguous depth ordering abolishes adaptation in LO (Kourtzi and Kanwisher 2001). James et al (2002) employed the adaptation method to argue that visual representations are more viewpoint dependent in posterior parietal cortex than in LO. Finally, Vuillemier et al (2002) have reported that, whereas LO responses are not suppressed by different exemplars belonging to the same category, these within-category repetitions do reduce BOLD signal in the left prefrontal cortex. This result suggests that, in addition to shedding light on the selectivity of neurons in visual cortex, MR adaptation might be useful for probing the neural substrates of semantic representations.

MR adaptation in relation to behavioral priming.

We have reviewed the nature of behavioral priming induced by stimulus repetition in humans. We also discussed the evidence that stimulus repetitions induce reductions in brain activity in the human brain. These two findings naturally lead to the speculation that priming at the behavioral level is mediated by reductions in brain activity (Wiggs and Martin 1998). In this section we review the evidence supporting this hypothesis.

A large number of studies have by now established that reductions in brain activity occur in humans during performance of behavioral priming tasks (e.g., Buckner et al 199x, Buckner et al 1998, van Turennout et al 2000, Dobbins et al 2004, Wig et al 2005). Moreover, the adaptation effects that accompany behavioral priming display many of the properties that are characteristic of priming. With regard to duration, both priming and MR adaptation effects are observable several days after induction (van Turennout et al 2000), and both effects have been shown to diminish together as the lag between the initial and repeat stimulus presentations is increased (Henson et al 2004). Furthermore, both behavioral and neural effects of stimulus repetition are cumulative over multiple presentations (van Turennout et al 2003).

In one study comparing the effects of two different tasks, one requiring explicit recall of previously viewed material and the other requiring a stimulus judgment independent of stimulus history, MR adaptation in LO was not observed in the explicit memory condition (Henson et al 2002, Wagner et al 2000). This result raises the possibility that the transient nature of repetition suppression in IT neurons that some groups have reported may be attributable to the use of an explicit memory task (Baylis and Rolls 1987, Sobotka and Ringo 1993). In addition to the

human visual region LO, BOLD signal reductions have also been reported in frontal regions during priming tasks. In some cases the magnitude of MR adaptation is actually greater in prefrontal cortex than in visual cortex (Buckner et al 1998, Maccotta and Buckner 2004, Dobbins et al 2004), probably on account of a component of semantic processing required by the tasks employed in these studies.

Is there a causal link between MR adaptation and priming?

These results establish that decreases in brain activation do indeed accompany performance of behavioral priming tasks - a necessary, if not sufficient, requirement for a functional relation between the two phenomena. A further requirement is that the magnitude of behavioral priming be correlated with the magnitude of accompanying BOLD signal suppression. Ideally, this relation should be assessed on the basis of responses to individual stimuli, but unfortunately results from such an analysis are not yet available for imaging data. However, three recent studies have assessed the correlation between priming and MR adaptation across subjects (Dobbins et al 2004, Maccotta and Buckner 2004, Sayres and Grill-Spector 2005). Significantly, these studies have *not* demonstrated a consistent positive correlation between behavioral priming and BOLD signal decreases in LO. However, two tasks did demonstrate a positive correlation in prefrontal cortex. In one study, the subjects performed a word-stem completion task, which is known to strongly engage prefrontal cortex (Maccotta and Buckner 2004). The other study required the subjects to switch between two modes of behavioral response between prime and probe trials, which again places processing demands on prefrontal cortex. A relation between priming and adaptation has recently been demonstrated with trans-cranial magnetic stimulation (TMS). In this study, TMS was applied specifically to the frontal region that undergoes activity

reductions in a priming task involving semantic processing. This stimulation was found to disrupt both behavioral priming and MR adaptation in prefrontal cortex (Wig et al 2005). This study indicates that a connection exists between behavioral priming and activity reductions in frontal cortex, at least for tasks that make demands on semantic processing. Thus far, it remains to be demonstrated that MR adaptation in LO correlates with priming of perceptual priming. Such a demonstration may require the use of tasks that are less contaminated by semantic components than have commonly been employed in fMRI studies of repetition priming (e.g., Buckner et al 1998, Henson et al 2003, Sayres and Grill-Spector 2005).

3.2.5 Is repetition suppression the neural basis of repetition priming?

Thus far, we have established that stimulus repetitions result in (1) behavioral priming effects in humans, (2) neuronal suppression effects in monkey IT, and (3) reductions in BOLD signal in human visual region LO. Moreover, (4) decreases in brain activity in LO have been demonstrated to occur under the same conditions that induce behavioral priming. These four lines of evidence have supported the idea that repetition priming at the behavioral level is mediated by firing rate decreases at the level of single neurons (Ungerleider et al 1995, Desimone 1996, Wiggs and Martin 1998, Henson et al 2003, Grill-Spector et al, in press). However, it has never been demonstrated that repetition suppression of single neurons in monkey IT accompanies behavioral priming; indeed, repetition priming has never been demonstrated in monkeys. Thus the link between behavioral priming and cellular activity depends on assuming (1) a correspondence between firing rate reductions in neurons and decreases in cerebral blood flow, and (2) a correspondence between behavior and brain activity between humans and monkeys. The first assumption is questionable, in that the BOLD signal is more strongly

correlated with synaptic activity than with action potentials (Logothetis et al 2001). Moreover, it is somewhat paradoxical that decreases in brain activity might result in an improvement in perceptual processing. Indeed, biologically plausible models of priming effects make the opposite prediction, namely that increases in neural activity should accompany priming (Stark and McClelland 2000).

How does repetition influence stimulus selectivity in IT?

Attempts to reconcile this apparent contradiction have led to the proposal of the **sharpening hypothesis** (Li et al 1993, Ungerleider 1995, Desimone 1996, Wiggs and Martin 1998), the essential prediction of which is illustrated by the case of a hypothetical neuron in Figure 11A. According to the sharpening hypothesis, the effect of repetition suppression is not equivalent across all repeated stimuli. Rather, neural responses to stimuli that are highly effective at driving the cell (i.e., stimuli near the peak of the hypothetical tuning curve in Figure 11A) undergo little or no suppression. In contrast, stimuli that are only marginally effective undergo significant suppression. Consequently, the neuron will discriminate more clearly between its preferred and non-preferred stimuli as a result of prior experience, and therefore the neuron will contribute to faster and more efficient perceptual processing. The sharpening hypothesis provides an intuitively compelling account of how suppression might be linked to behavior. Evidence that neural representations in IT can become sharpened as a result of extensive training over long time periods comes from studies of expertise learning (Rainer and Miller 2000, Baker et al 2002, Rainer and Logothetis).

However, it has not been demonstrated that sharpening of neural selectivity results from repetition suppression. Indeed, the little available evidence points in the opposite direction, which we will refer to here as the **scaling hypothesis** (Li et al 1993, Avidan et al 2002, Grill-Spector and Malach 2001, reviewed by Grill-Spector et al 2005). The essential prediction of the scaling hypothesis is illustrated by the case of the hypothetical neuron shown in Figure 11B. According to the scaling hypothesis, the magnitude of repetition suppression is a constant proportion of initial stimulus efficacy. Accordingly, the magnitude of responses are reduced uniformly as a result of stimulus repetition, and the shape of the tuning curve remains unchanged. This proposal is based on two observations reported by Li et al (1993). First, the neurons in which the strongest suppression was observed tended to be the same neurons which had the strongest initial responses. Second, the set of novel stimuli, which tended to evoke stronger initial responses than the set of familiar stimuli, also tended to undergo stronger suppression. If we make the assumptions that (1) the trend in mean visual responses observed across different neurons also holds true across different stimuli within individual neurons, and (2) the greater suppression induced by repeated novel stimuli is attributable to their greater efficacy in evoking a visual response, rather than their novelty per se, then it follows that the effect of repetition suppression would at least qualitatively resemble what is shown in figure 11B. A major goal of the experiment described in this chapter is to determine which of these two models better accounts for the pattern of repetition suppression induced in repetition priming task.

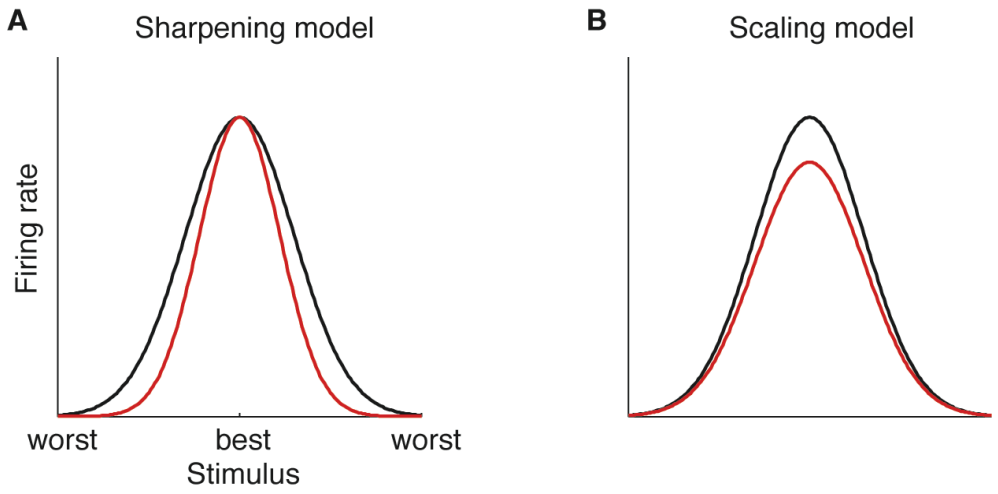


Figure 11. Alternative models of repetition suppression. Each curve illustrates the tuning profile of a hypothetical neuron before (black lines) and after (red lines) stimulus repetition. **(A)** The sharpening model predicts that repetition induces little or no suppression for the most effective stimulus. **(B)** In contrast, the scaling model predicts that suppression is a constant proportion of the original stimulus efficacy.

3.2.6 Experimental aims

We conclude this background session by reiterating the gaps in our understanding of the mechanisms of repetition priming. The prevailing hypothesis in the field is that repetition suppression mediates behavioral priming via a mechanism of selectivity sharpening. However, repetition suppression has never been demonstrated to occur in the context of a behavioral priming task; indeed, priming has not been demonstrated in monkeys. Furthermore, it is not known how stimulus selectivity is affected by repetition suppression. To address these gaps in our current knowledge, we developed a monkey model of repetition priming. We then used this model to address the following four specific aims: (1) Do the behavioral responses of monkeys undergo repetition priming? (2) In the context of a behavioral priming task, do the visual responses of IT neurons undergo repetition suppression? (3) Do the behavioral and neuronal effects of stimulus repetition covary? (4) How does repetition suppression affect the stimulus selectivity of IT neurons?

3.3. Methods

Recording location.

The recording locations were in anterior IT in the right hemisphere of two monkeys (EG and PH). Recording chambers in both monkeys were centered at Horsley-Clarke coordinates (18

anterior and 18 lateral). Physiological recordings were obtained primarily from the ventral convexity of area TE near the perirhinal sulcus, and in the lower bank of the superior temporal sulcus.

Task Design.

Both monkeys were trained to perform the task diagrammed in Figure 12A. The monkey initiated each trial of the task by fixating within approximately 2° of a central white dot. After a 200 ms fixation interval a stimulus appeared at the center of the screen. The stimulus was either symmetrical or asymmetrical across the vertical mid-line. Simultaneously with stimulus onset, two white target dots appeared 4.8 deg. above and below the horizontal mid-line. Monkey EG was rewarded for making a saccade to the upper target if the stimulus was symmetrical, or to the lower target if the stimulus was asymmetrical. The association between symmetry and saccade direction was reversed for monkey PH. Incorrect trials were followed by a pause of 1200 ms.

Sixty symmetrical and 60 asymmetrical stimuli were presented two times each over the course of a single session, for a total of 240 trials. The order of stimulus presentation was constrained so that the lag between the first and second presentations of every stimulus was either 0, 1, 2, 4, 8, or 16 intervening different stimuli (Figure 12B). The number of consecutive runs of the same stimulus type (either symmetrical or asymmetrical) was constrained to be consistent with the runs generated by a binomial process, so that the correct response on any given trial was independent of the correct response on any other trial. In order to generate sequences that satisfied these criteria in an efficient manner, we developed a recursive algorithm that randomly generated segments of 24 trials, containing 12 symmetrical and 12 asymmetrical trials that

included repeats at all six lags. Ten different such segments were then concatenated together to produce the sequence for a single experimental session.

Stimulus design.

Each white stimulus consisted of a central bar 0.5° wide and 2.3° high, a right-side flanking shape and a left-side flanking shape. The entire stimulus, consisting of the central bar and the flanking shapes, fit within a 2.3° by 2.3° square. The purpose of the central bar was to prevent local feature differences in the left- and right-hand flanking shapes from laying immediately adjacent to one another (in the case of asymmetrical stimuli), thus requiring the monkeys to perform the task on the basis of global structure, rather than local stimulus features near the midline. For each session, a new set of 120 stimuli was constructed by random selection without replacement from a library of 180 available right-side flanking shapes. From 60 of these shapes were constructed 60 symmetrical stimuli, each consisting of the central bar, the right-side shape (on the right) and its mirror image (on the left). From the remaining 120 shapes were constructed 60 asymmetrical stimuli, each consisting of the central bar, one right-side shape (on the right) and the mirror image of another right-side shape (on the left). This procedure ensured that the monkeys were exposed to all flanking shapes with equal frequency and that all flanking shapes had the same probability of being contained in a symmetrical vs. an asymmetrical stimulus. However, it led to the consequence that, across multiple sessions, symmetrical stimuli tended to recur whereas asymmetrical ones did not. This followed from the fact that there were only 180 possible symmetrical images, whereas there were 32,220 possible asymmetrical images.

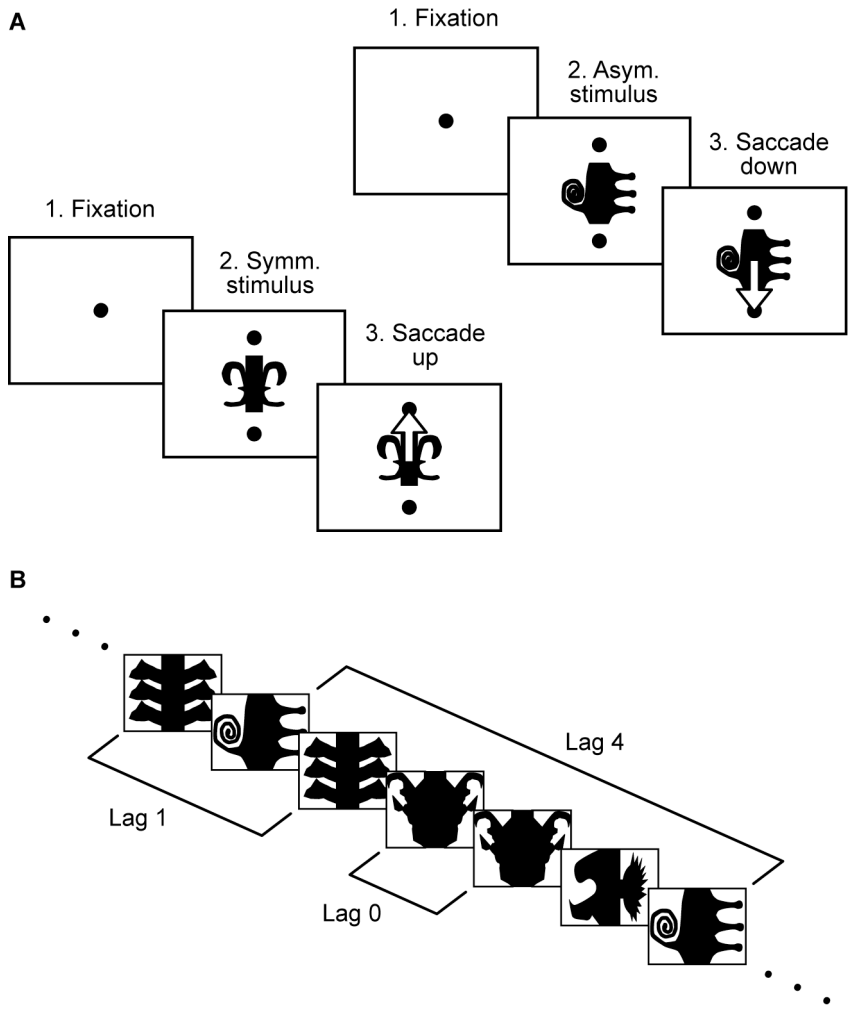


Figure 12. (A) Sequence of events in the symmetry decision task. The monkey initiated each trial by fixating on a white dot in the center of the screen. After 200 ms, a central stimulus and an upper and lower saccade target appeared. Monkey EG was rewarded for making an upward saccade if the stimulus was laterally symmetrical, or a downward saccade if the stimulus was asymmetrical. Monkey PH learned the opposite association. **(B)** Sample trial sequence illustrating stimulus repetitions. An experimental session consisted of 240 trials, over the course of which 60 symmetrical and 60 asymmetrical stimuli were presented two times each. The lag between first and second presentations of a given stimulus was always either 0, 1, 2, 4, 8, or 16 intervening trials. The inter-stimulus interval was approximately 1.9 seconds. Ten symmetrical and ten asymmetrical stimuli were repeated at each of the six lags. A new set of stimuli was generated for each session so as to avoid over-training on particular stimuli.

3.4. Results

3.4.1 Behavioral effects of stimulus repetition

The purpose of this section is to characterize a primate model of priming. In pursuit of this objective, we describe the behavioral results obtained from two monkeys trained to perform the symmetry decision task described in the previous section. First, we will describe the basic performance of the subjects in terms of percent correct, reaction time, and bias. Second and most critically, we will assess the degree of reaction time priming induced by stimulus repetition. We will consider the influence of several experimental factors on priming, specifically lag, subject, and stimulus type. Finally, we will assess the contribution of response repetition to the observed priming effects.

Example of behavioral responses from a single session.

Behavioral data were collected over a total of 118 behavioral sessions (67 in EG, 51 in PH). Figure 13 provides an example of all behavioral responses collected within a single experimental session from monkey EG, presented in the format of vertical eye-position as a function of time after stimulus onset. Four noteworthy trends are succinctly illustrated in this figure, which will be noted briefly here and scrutinized more closely in the subsequent sections. First and most importantly, the monkey performed the symmetry discrimination with a high degree of accuracy, as is evident from the fact that the vast majority of black lines (from trials on which a

symmetrical stimulus) and blue lines (asymmetrical stimuli) indicate upward and downward saccades, respectively. Second, although the monkeys were rewarded for responses as late as 1000 msec after stimulus onset, they invariably responded considerably earlier. The monkeys were presumably motivated to respond quickly so as to maximize their rate of reward collection. These two preliminary observations are important in that they establish that the monkeys are capable of performing the symmetry decision task, and that they are motivated to respond as quickly as possible. Third, there was a consistent bias to respond "symmetrical", which was reflected in both the accuracy (percent correct: symm: 81.9%, asym 76.9%) and speed (RT_{symm} = 313 msec, RT_{asym} = 347 msec) of responses. This bias in favor of symmetrical responses, in addition to being of interest in its own right, indicates that behavioral effects will have to be assessed for stimuli of both types separately. Finally, the degree of RT variability across trials was extremely high (pooled standard deviation = 50.7 msec) in this session, which is of the same order of magnitude to the actual latency of response. High variability is typical in RT tasks even when subjects are motivated to respond quickly, and has been linked to variance in the rate of buildup of activity in neurons in frontal cortex (Hanes and Schall 1996). Finally, the high degree of variance in RTs emphasizes that priming effects are not likely to be detectable at the level of individual stimuli or individual sessions. Accordingly, our analysis of repetition priming will focus on population data pooled across all available sessions.

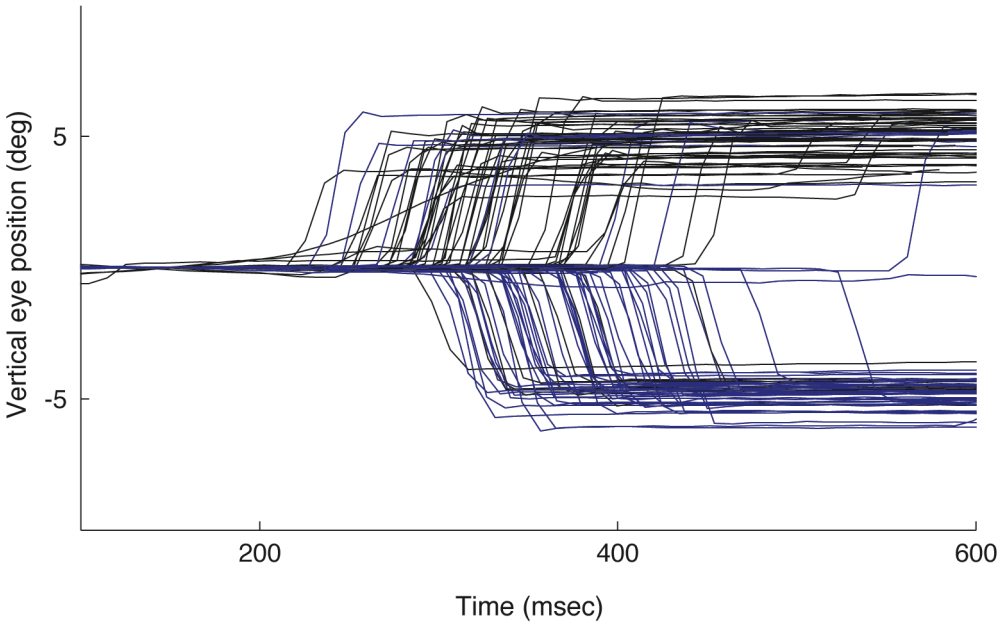


Figure 13. Eye traces from monkey EG, obtained during a single experimental session. Vertical eye position (y axis) is plotted as function of time (x axis). Each line represents data from a single trial, in which the monkey made a saccade either upward (to indicate a judgment of 'symmetrical') or downward (to indicate 'asymmetrical'). Black lines are from trials in which the stimulus was symmetrical, blue from asymmetrical.

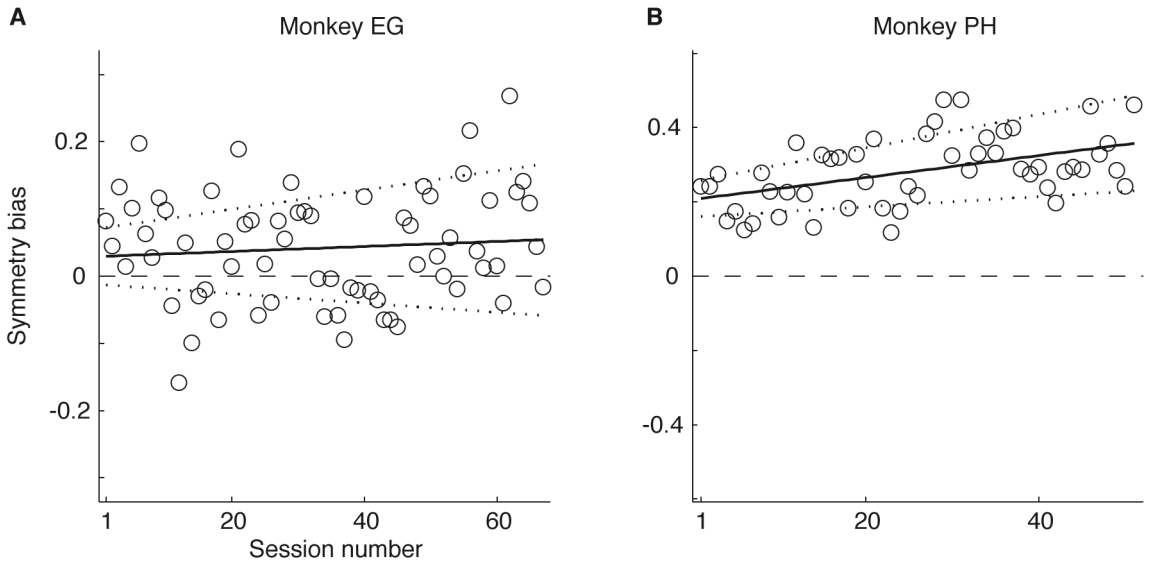


Figure 14. Trend analysis of response bias over experimental sessions for monkey EG **(A)** and monkey PH **(B).** Data are shown separately for each monkey. The x axis indicates session number, and the y axis indicates the monkey's bias for responding more rapidly to symmetrical as compared to asymmetrical stimuli. Bias is defined as the difference in the rate of correct responses on symmetrical vs. asymmetrical stimuli [p(s|S) - p(a|A)]. Positive values indicate a greater likelihood of the monkey responding "symmetrical". Each point represents the average symmetry bias for a given experimental session. Regression lines (solid) and 95% confidence intervals (dotted) show that monkey EG had no significant increase in symmetry bias as a function of session. The symmetry response bias was present in both monkeys even in the earliest sessions, when symmetrical and asymmetrical stimuli were equally familiar.

Response bias favoring symmetrical stimuli.

To determine whether there were systematic differences between behavioral responses to symmetrical as opposed to asymmetrical stimuli, we assessed both the percent correct and RT for both stimulus types separately. As the results in Table 2 indicate, both monkeys were more likely to respond "symmetrical." We quantified response bias according to the formula

$$B = p(s|S) - p(a|A),$$

where p(s|S) was the probability of correct responses to symmetrical stimuli, and p(a|A) was the probability of correct responses to asymmetrical stimuli. This definition had the property that bias could range from +1 if the monkey always responded "symmetric" to
-1 if the monkey always responded "asymmetric", and would be equal to 0 in the event of completely unbiased responses. Both subjects had a symmetry bias (+0.04 and +0.28, EG and PH), which was statistically significant in both cases ($p = 0.008$ and $p < 10^{-16}$, EG and PH, chi-squared test).

As the histograms of the RT distributions indicate (Figure 15), there was a strong RT bias such that responses were significantly slower to asymmetrical than to symmetrical stimuli (RT_{asym} - RT_{symm}:15 msec in EG, 127 msec in PH; $p < 10^{-10}$ in both subjects, two-sided Wilcoxon rank-sum test). This bias is consistent with the results of a previous study of symmetry decision in human subjects (Kersteen-Tucker 1991). Because symmetrical stimuli were more frequently encountered over the course of the entire experiment (see Methods), a similar familiarity effect might have contributed to the tendency for monkeys to respond faster to symmetrical stimuli, in addition to a symmetry response. To assess this possibility, we conducted a trend analysis of symmetry bias as a function of experimental session. Because the stimulus set used to train the monkeys was completely different from the set used for data collection, both symmetrical and asymmetrical stimuli were initially novel. As the symmetrical combinations were more frequently presented from one session to the next, they became more familiar than the asymmetrical combinations as the experiment progressed. Thus a trend towards increasing symmetry bias over session number would reflect a familiarity effect that could be distinguished from response bias attributable to symmetry per se. In EG, there was no significant trend in bias

over sessions ($r = 0.086$, $p = 0.49$), indicating that familiarity did not contribute to response bias (Figure 14). In PH, there was a significant familiarity effect ($r = 0.47$, $p = 4.5 \cdot 10^{-4}$), however a strong symmetry bias was clearly present at the outset of data collection (Figure 14B). The y-intercept of the regression line was significantly greater than zero (+0.21, $p = 1.4 \cdot 10^{-11}$), and was in close agreement with the mean symmetry bias over the first 5 sessions (+0.22). We conclude that both monkeys exhibited a response bias in favor of symmetry that was independent of stimulus familiarity.

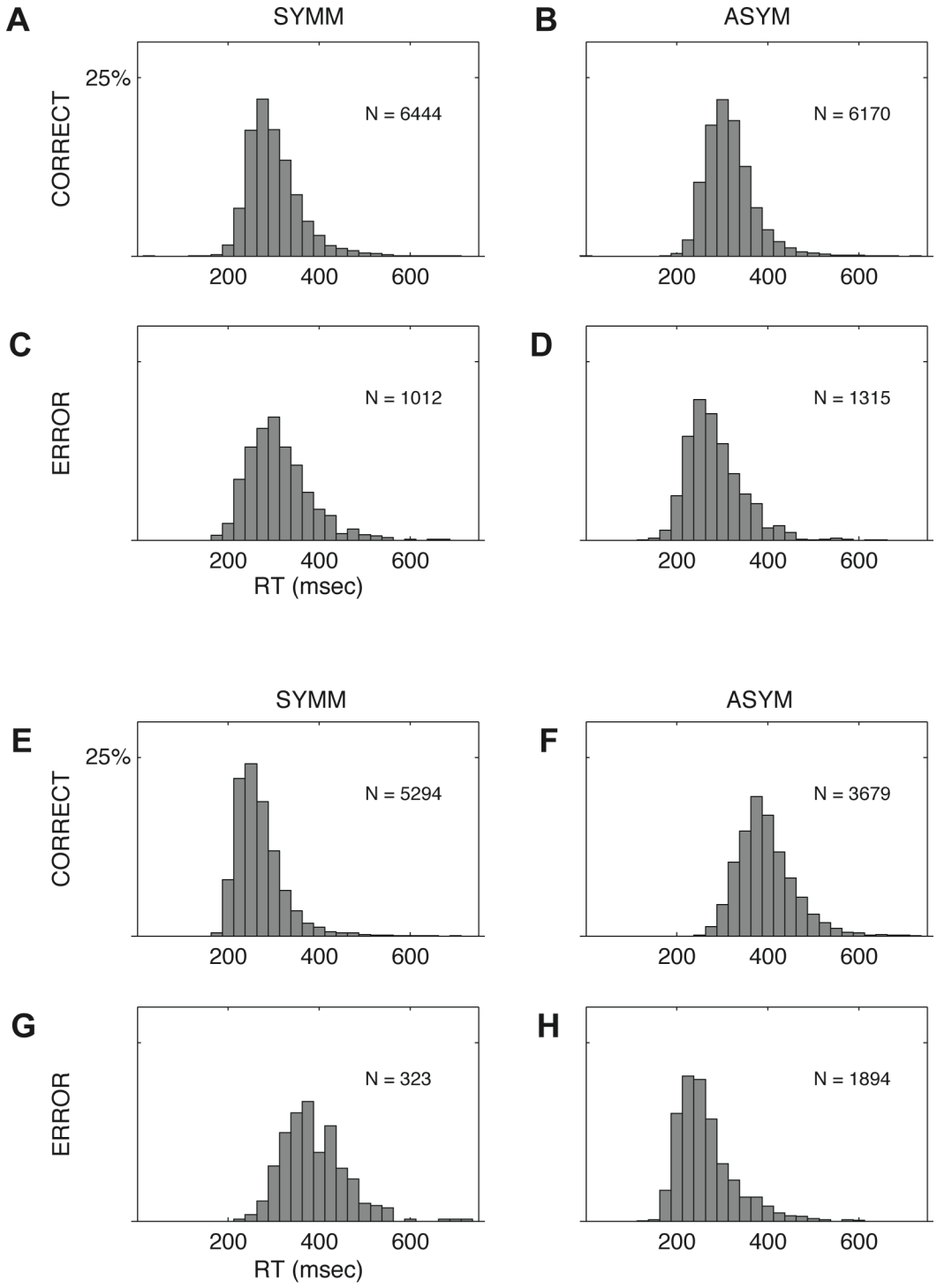


Figure 15. **(A-D)** Behavioral reaction time (RT) histograms for monkey EG. Responses are shown separately for symmetrical and asymmetrical stimuli, and for both correct and error responses. **(E-H)** Behavioral RT histograms for monkey PH.

Trend analysis of behavioral responses.

The assessment of priming effects will require pair-wise comparisons between responses to the first and second presentations of the same stimuli. For such comparisons, a critical assumption is that both first and second responses are sampled under stationary conditions. Accordingly, we conducted a trend analysis to assess the stability of both RT and firing rate as a function of trial number within the experimental session. Figure 16A displays the mean RT over all 118 behavioral sessions as a function of trial number. A linear regression analysis indicated that there was no significant change in RT between trials 1 and 240 ($R^2 = 0.01$, $p = 0.12$). However, closer inspection of the earliest trials revealed a transient decline in RT over the first few responses (Figure 16B). This training effect was not stimulus specific, and declined with an exponential time constant ($\tau_{RT} = 3.8$ trials) that was assessed using the equation

$$y = A \cdot \exp(-x/\tau) + C,$$

where x represents trial number and y represents mean RT across sessions. In order to restrict our analysis of behavioral priming and neuronal suppression effects to stationary epochs, we excluded the first 12 trials from all subsequent analyses that required comparisons between initial and repeat presentations of the same stimulus.

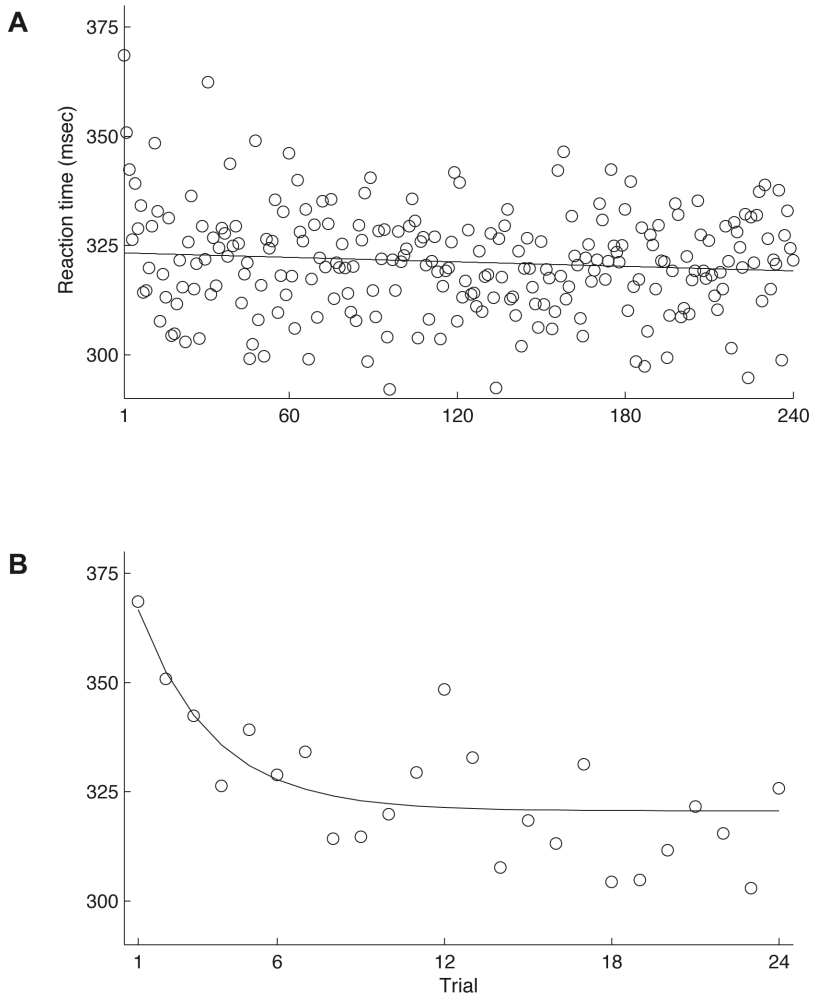


Figure 16. **(A)** Mean behavioral reaction time as a function of trial number within a session. Each point represents the average RT over all 89 sessions. Black line: linear regression fit. **(B)** Mean reaction times for the first 24 trials on an expanded time scale. Black line: fit of exponential decay function.

Effects of stimulus repetition on reaction time: repetition priming.

Due to the high degree of trial-to-trial variance in RT discussed in sections (1) and (2) above, we assessed priming effects at the population level by pooling responses together across experimental sessions. Priming was defined as the pair-wise RT difference for each stimulus (RT_1 - RT_2). Stimuli were excluded from this analysis if the monkey did not respond correctly to both first and second presentations. The first 12 trials of each session were also excluded, as noted in section (3) above. This filtering procedure yielded between 1434 and 1500 paired stimulus presentations at each lag (mean = 1461). Critically, in these trials, there was a robust effect of repetition, in that the RT in response to the second presentation of the stimulus was shorter on average in both monkeys (Figure 17A). This effect was highly significant at all lags ($p < 5 \cdot 10^{-3}$, one-sided Wilcoxon signed-rank test) and especially at lag 0 ($p = 1 \cdot 10^{-24}$). The magnitude of priming at each lag is listed for each monkey and each stimulus type separately in table 3. To assess the contribution of specific experimental parameters to the priming effect, we conducted a 3-way ANOVA on RT_1 - RT_2 that modeled the factors **lag** (0, 1, 2, 4, 8, or 16), stimulus **type** (symmetrical or asymmetrical), and **monkey** (EG or PH). The results of this ANOVA are summarized in Table 3. There were highly significant main effects of all three factors. The main effect of **lag** was due to the particularly strong effect at lag 0, which was significantly higher than all other lags. Lags 1 through 16 did not differ among themselves, as determined by a Tukey post-hoc test. The main effects of both **monkey** and **type** reflected the fact that priming tended to be much stronger in monkey EG (Figure 17A) and for symmetrical stimuli (Figure 17B), These effects were themselves lag dependent, as indicated by significant interaction effects **lag** x **type** and **lag** x **monkey**, on account of a preferentially greater lag 0

priming effect in monkey EG and for symmetrical stimuli (Tukey test). We conclude that the symmetry decision task induces robust behavioral priming in monkeys. The priming effect was observable in both subjects and for both symmetrical and asymmetrical stimuli.

Results from a 3-way anova on priming effects

BEHAVIOR

Source	**d.f.**	**Sum Sq.**	**Mean Sq.**	**F-statistic**	**p-value**
lag	5	8.26E+04	1.65E+04	3.7008	0.0024
type	1	5.42E+04	5.42E+04	12.1427	0.0005
monkey	1	2.60E+04	2.60E+04	5.8251	0.0158
lag*type	5	1.21E+05	2.43E+04	5.4312	0.0001
lag*monkey	5	6.33E+04	1.27E+04	2.8338	0.0146
type*monkey	1	1.24E+04	1.24E+04	2.7697	0.0961
lag*type*monkey	5	1.60E+04	3.21E+03	0.718	0.6099
Error	11203	5.00E+07	4.47E+03		
Total	11226	5.05E+07			

Table 2. Results from a multi-factor ANOVA assessing the effects of three factors on reaction time differences between prime and probe stimuli. The three factors were: **lag** (0,1,2,4,8, or 16), stimulus **type** (symmetrical or asymmetrical), and **monkey** (EG or PH).

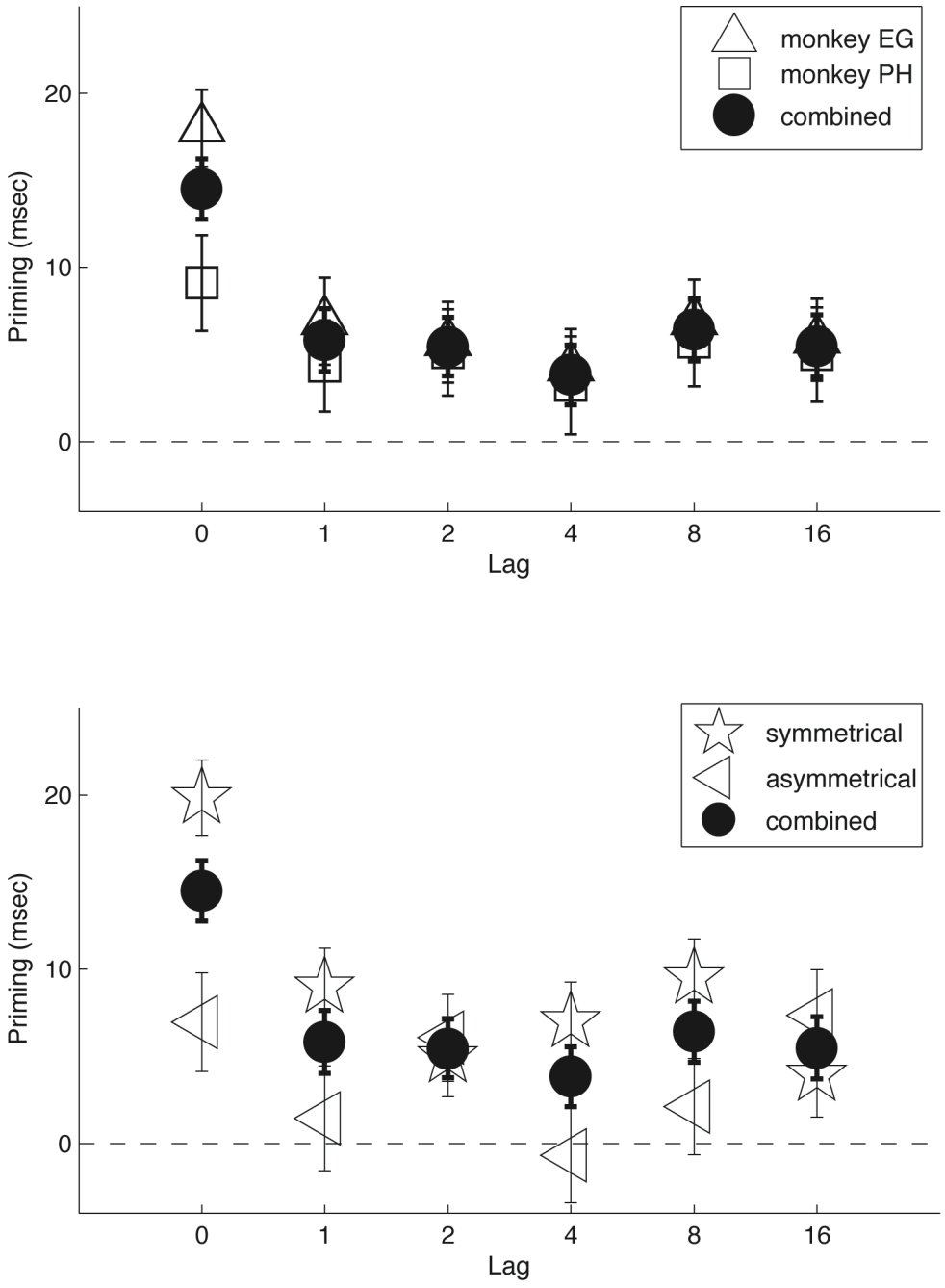


Figure 17. (A) Behavioral priming as a function of lag, averaged across 118 sessions. Data are shown for monkey EG and PH separately. Priming was defined as the pair-wise difference in reaction time between first and second presentation of each stimulus (RT_1 - RT_2). Stimuli to which the monkey did not respond correctly on both presentations were excluded from analysis. Each point represents the average priming at each lag, based on 1434 to 1500 pairs of stimulus presentations (mean = 1461 stimuli). **(B)** Priming effect for symmetrical and asymmetrical stimuli.

Strength and statistical significance of repetition priming effects

	Lag	Priming (ms)	p-value	N pairs
Monkey EG	**0**	18.0	5.10E-21	884
	1	6.9	3.38E-05	837
	2	5.7	0.0015	850
	4	4.3	0.0237	823
	8	6.9	6.24E-04	848
	16	5.8	0.0049	836
Monkey PH	**0**	9.1	3.01E-06	568
	1	4.3	0.1369	618
	2	5.1	0.0085	650
	4	3.2	0.0256	611
	8	5.7	0.0047	623
	16	5.0	0.0363	618
Symmetrical	**0**	19.8	6.43E-25	852
	1	9.0	2.71E-06	844
	2	5.0	0.0013	847
	4	7.0	1.25E-04	843
	8	9.5	1.15E-06	857
	16	3.9	0.0406	794
Asymmetrical	**0**	6.9	7.67E-05	600
	1	1.4	0.292	611
	2	6.1	0.0078	653
	4	-0.7	0.492	591
	8	2.1	0.1926	614
	16	7.4	0.0029	660

Table 3. Summary of behavioral priming effects, defined as (RT_1 - RT_2). Priming was statistically significant for 20 out of 24 comparisons ($p < 0.05$, signed-rank tests). Priming values are given separately for each lag (0 through 16), monkey (EG and PH, collapsed across stimulus type), and stimulus type (symmetrical and asymmetrical, collapsed across monkey).

Effects of response repetition on reaction time: inhibition of return.

Because two presentations of the identical stimulus necessarily called for eye movement responses in the same direction in response to both presentations, the priming effects described thus far could in principal be due to either stimulus repetition or to response repetition. To assess whether response repetition contributed to the priming effects displayed in Figure 18, we adapted the method of memory kernel analysis from Maljkovic and Nakayama (1994). Our procedure was as follows: mean RTs were obtained from trials that were divided into different groups defined as $TYPE_{antecedent}$, which were defined on the basis of whether the stimulus type (symmetrical or asymmetrical) presented on the preceding trial matched the stimulus type presented on the current trial. Identical stimulus repeats were excluded from this analysis. The four groups thus defined were $SYMM_{same}$, $SYMM_{different}$, $ASYM_{same}$, and $ASYM_{different}$ (for instance, the group $SYMM_{same}$ consisted of all trials on which a symmetrical stimulus was preceded by a non-identical stimulus that was also symmetrical). Trials were excluded from analysis if the monkey did not respond correctly on both the current and the antecedent trials. This procedure was repeated for antecedents at all lags from 0 to 16. The mean effect of response repetition at each lag, defined as mean of ($SYMM_{different}$ - $SYMM_{same}$) and ($ASYM_{different}$ - $ASYM_{same}$), is displayed separately for each monkey in Figure 18. There was only a significant effect of response repetition for lags 0 and 1 (rank-sum tests, with Bonferroni correction). At these two shortest lags, we observed a small inhibition of return effect (Bichot and Schall 2002), as opposed to the response priming effect that has been reported in priming of pop-out studies (Maljkovic and Nakayama, 1994, Walsh et al, 2000, Dorris et al, 1999). We conclude that the priming effects reported in the previous section are entirely due to stimulus repetition, as distinct from response repetition.

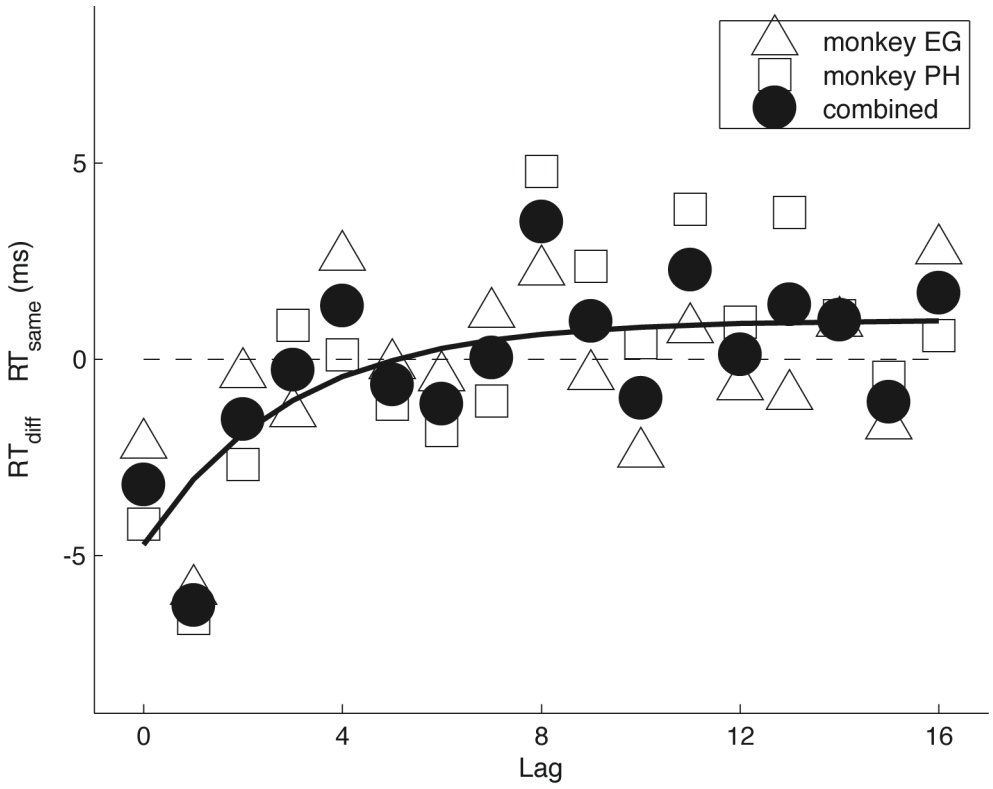


Figure 18. Response priming for both monkeys as a function of lag. Response priming is distinct from repetition priming and is defined as (RT_{diff} - RT_{same}). RT_{diff} is the reaction time on trials where the motor response was opposite the response required on the previous trial (e.g. a downward saccade trial that was preceded by an upward saccade trial). RT_{same} is the reaction time on trials where the motor response was the same as on the previous trial. Thus a positive value for (RT_{diff} - RT_{same}) indicates faster RT following antecedents calling for the same response. The repetition of the same motor response at early lags actually induced *longer* RTs, as indicated by the negative values at lags 0 and 1.

Summary.

The behavioral results reported in this chapter demonstrate that (1) monkeys are capable of distinguishing symmetrical stimuli from asymmetrical stimuli, and (2) that stimulus repetition results in priming of reaction times. Behavioral priming was lag dependent, and observed in both monkeys and for both stimulus types. We established that motor response repetition did not contribute to the observed speeding of reaction times, which were therefore concluded to be entirely due to stimulus repetitions per se. Our findings could be accounted for by a mechanism of facilitation at the level of perceptual processing itself, or by a strengthening of the association between a given stimulus and the correct response (Dobbins et al 2004), or by some combination of these two mechanisms. Having established a primate model of repetition priming, we are now able to proceed to the next critical question: Do visual responses in IT undergo repetition suppression in the context of a behavioral priming task?

3.4.2 Physiological effects of stimulus repetition

The purpose of this section is to assess the effects of stimulus repetition on the visual responses of single neurons in IT in the context of the symmetry decision task. Because we are ultimately interested in the effect of stimulus repetition selectivity tuning, we will first characterize the stimulus selectivity of single neurons observed under our conditions. Selectivity will be considered both for individual stimuli, and for symmetrical as compared to asymmetrical stimuli. Second and most critically, we will test whether stimulus repetition induces neuronal suppression. We will assess the contributions of lag, subject, and stimulus type on repetition suppression. Finally, we will assess the effect of repetition suppression on the time-course of neuronal responses in IT.

Example of physiological responses from a single neuron.

An example of visual responses from a single neuron (from monkey EG) to 78 different stimuli is illustrated in Figure 19 (Only stimuli to which the monkey responded correctly on both presentations were included). The raster plots, sorted in descending order from the most to least effective stimulus, emphasize an important aspect of our experimental design: Unlike a typical IT experiment, in which a small number of stimuli are pre-screened for efficacy and then used to collect visual responses across multiple trials, we sampled each neuron's visual responses over a large set of unscreened stimuli. This procedure spontaneously resulted in a broad range of response magnitudes, since some of the stimuli happened to drive the cell extremely well and others poorly or not at all. This heterogeneity of visual responses will play an important role later when we assess the effect of repetition on stimulus selectivity. More importantly, it raises the question of what constitutes a real response and what's noise. In the analysis throughout this

section, we adopted the most permissive filtering criteria possible, which was to regard any stimulus that evoked at least one spike on either the first or the second presentation as a putatively effective stimulus. While this filtering criterion undoubtedly resulted in a certain amount of noise, it is also extremely conservative in that it does not depend on any assumptions about the expected magnitude of a true visual response.

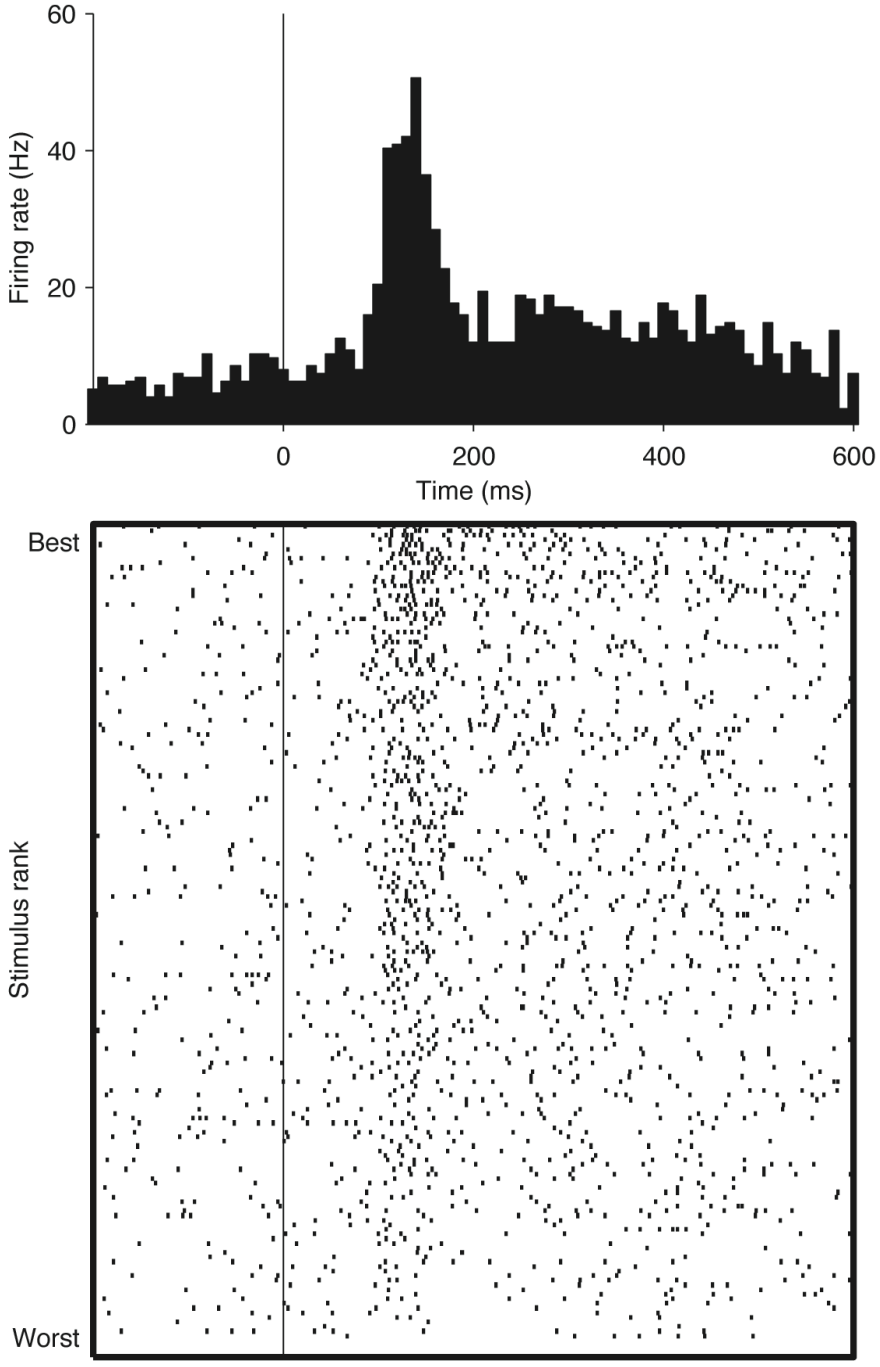


Figure 19. Responses of a single neuron from monkey EG to 78 different visual stimuli. Two visual responses were collected for each stimulus. Top panel shows the instantaneous firing rate histogram averaged across all stimuli. Bottom panels show raster traces for each trial, sorted from best to worst stimulus.

Neural selectivity for individual stimuli.

Because IT neurons respond to visual objects with complex structure in a manner that is seldom possible to predict, measuring selectivity in IT poses unique challenges. In earlier visual areas, it is often possible to characterize selectivity as a parametric firing rate function along the feature dimension to which the neuron is sensitive. In IT however, stimulus selectivity can only be defined relative to a given object set. We characterized selectivity as the distribution of mean firing rates evoked for each stimulus that was presented. Figure 20 displays the selectivity profile (referred to as a spike-count distribution) for the same neuron shown in Figure 19. It is desirable to express the degree of selectivity for a spike-count distribution in terms of a single variable. A convenient metric for summarizing selectivity is sparsity, defined as

$$S = \frac{\left(\sum \frac{r_i}{N}\right)^2}{\left(\sum \frac{r_i^2}{N}\right)},$$

where r is the neuron's response to each stimulus, and N is the total number of stimuli presented (Treves and Rolls 1992). This definition has the property that a completely uniform spike-count distribution will have a value of 1, whereas a neuron that responds to only one stimulus out of 100 will have a sparsity of 0.01. Thus values close to zero indicate greater stimulus selectivity. The sparsity obtained for the spike-count distribution shown in Figure 20 was 0.77. Figure 21 summarizes the distribution of sparsity values obtained from spike-count distributions of 152 neurons. The mean sparsity for the entire population was 0.65, which is comparable to previous studies of IT selectivity that used the same metric (Rolls and Tovee 1995, Young and Yamane 1992).

Figure 20. Spike-count distribution for an example single neuron in IT. Neural activity (y axis) is shown for all visual stimuli, ordered according to stimulus rank: firing rates are shown for the worst stimuli (far left) to the best stimuli (far right). In this format, a highly selective neuron would have high firing rates only for the best stimuli (skewed right). The selectivity tuning of this spike-count distribution is relatively broad, as reflected by its sparsity value (S = 0.77). Sparsity ranges values near 0 (sharp tuning) to values near 1 (broad tuning).

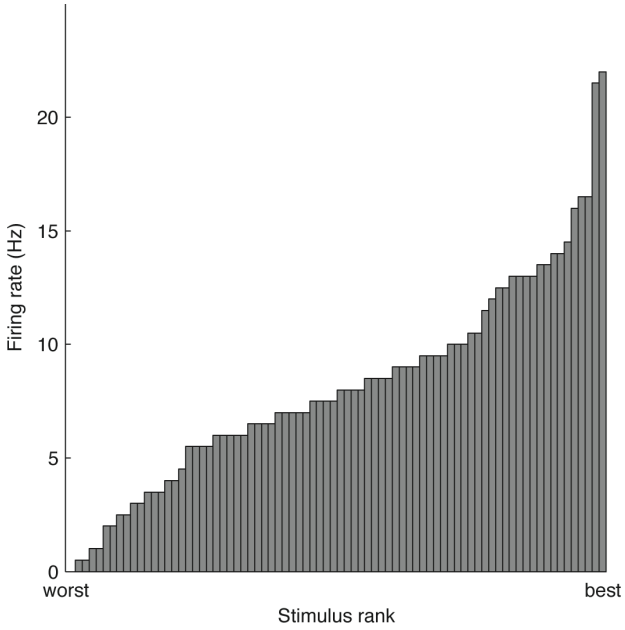
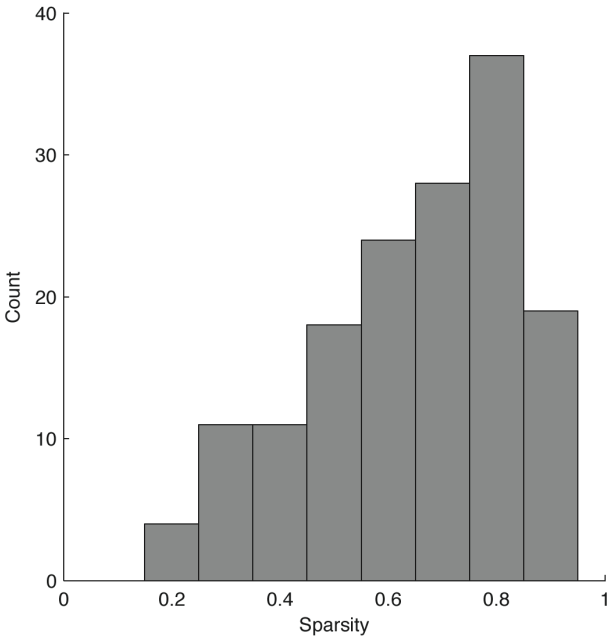


Figure 21. Distribution of sparsity values for a population of 152 IT neurons. Sparsity values near 1 indicate that a neuron had greater selectivity for a particular visual stimulus, whereas sparsity values near 0 indicate that a neuron responded similarly for all visual stimuli. The distribution is skewed toward 1, demonstrating that the population of IT neurons is relatively broadly tuned.



Neuronal responses to symmetrical vs. asymmetrical stimuli.

To determine whether IT neurons had consistently different responses to symmetrical and asymmetrical stimuli, we compared neuronal firing rates evoked by symmetrical and asymmetrical stimuli (FR_{symm} and FR_{asym}) within a window of 80 to 280 ms following stimulus onset. (Trials on which the monkey generated both correct and incorrect responses were included in this analysis.) Symmetrical stimuli tended to evoke stronger responses from IT neurons than did asymmetrical stimuli ($p = 0.001$, two-sided Wilcoxon rank-sum test, Figure 22). On average, responses to symmetrical stimuli were 3.1% greater than responses to asymmetrical stimuli (3.6% for EG and 2.6% for PH). There was no significant difference between correct and incorrect responses to stimuli of either type. This result is compatible with recent findings that symmetrical stimuli evoke stronger BOLD responses in both human and monkey ventral visual cortex (Tyler et al 2005, Sasaki et al 2005). It is unlikely to be due to the difference in familiarity between symmetrical and asymmetrical images (see Methods) because familiarity results in weaker responses among IT neurons (Li et al 1993, Fahy et al 1993). Furthermore, there was no significant trend towards neural responses favoring symmetrical stimuli as a function of session number (EG: $r = 0.13$, $p = 0.36$; PH: $r = -0.14$, $p = 0.27$). A significant trend would be expected if the increasing familiarity of the symmetrical stimuli, rather than their symmetry in itself, had led to stronger responses. This symmetry bias may be related to the fact that IT neurons respond similarly to the two members of any given lateral mirror image pair (Rollenhagen and Olson 2000). Enhanced processing of symmetrical stimuli might serve a useful function in a natural environment, because symmetry detection has the potential to facilitate the structural interpretation of three dimensional objects (Vetter et al 1994).

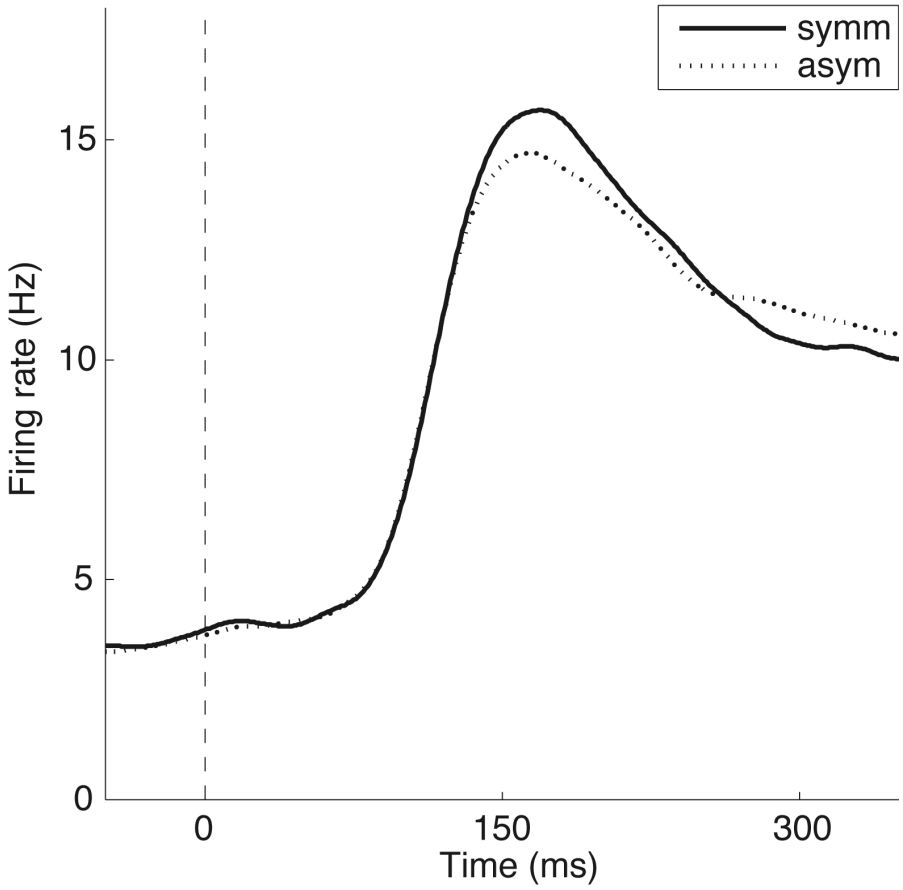


Figure 22. Spike density functions show average firing rate as a function of time, for symmetrical stimuli (solid line) and asymmetrical stimuli (dotted line). Neural activity in IT is stronger for symmetrical as compared to asymmetrical visual stimuli.

Trend analysis of neuronal responses.

Analysis of repetition suppression will be based on pair-wise comparisons between firing rates evoked on first and second stimulus presentations, a procedure which assumes that both responses were collected under stationary conditions. To ensure that this condition was met, we conducted a trend analysis to assess the stability of neuronal firing rate as a function of trial number within the experimental session. The procedure was entirely parallel to the trend analysis performed on reaction times (Figure 16), and the results were almost identical. There was no significant drift in neuronal response over the course of the entire session ($R^2 = 0.01$, $p = 0.10$, Figure 23A). However, a transient habituation effect was present at the beginning of the session. This effect, which was cell-specific rather than stimulus-specific, decayed with a time constant of $\tau_{FR} = 3.0$ trials (Figure 23B). Accordingly, we excluded the first 12 responses from each session in order to restrict our analysis to stationary epochs.

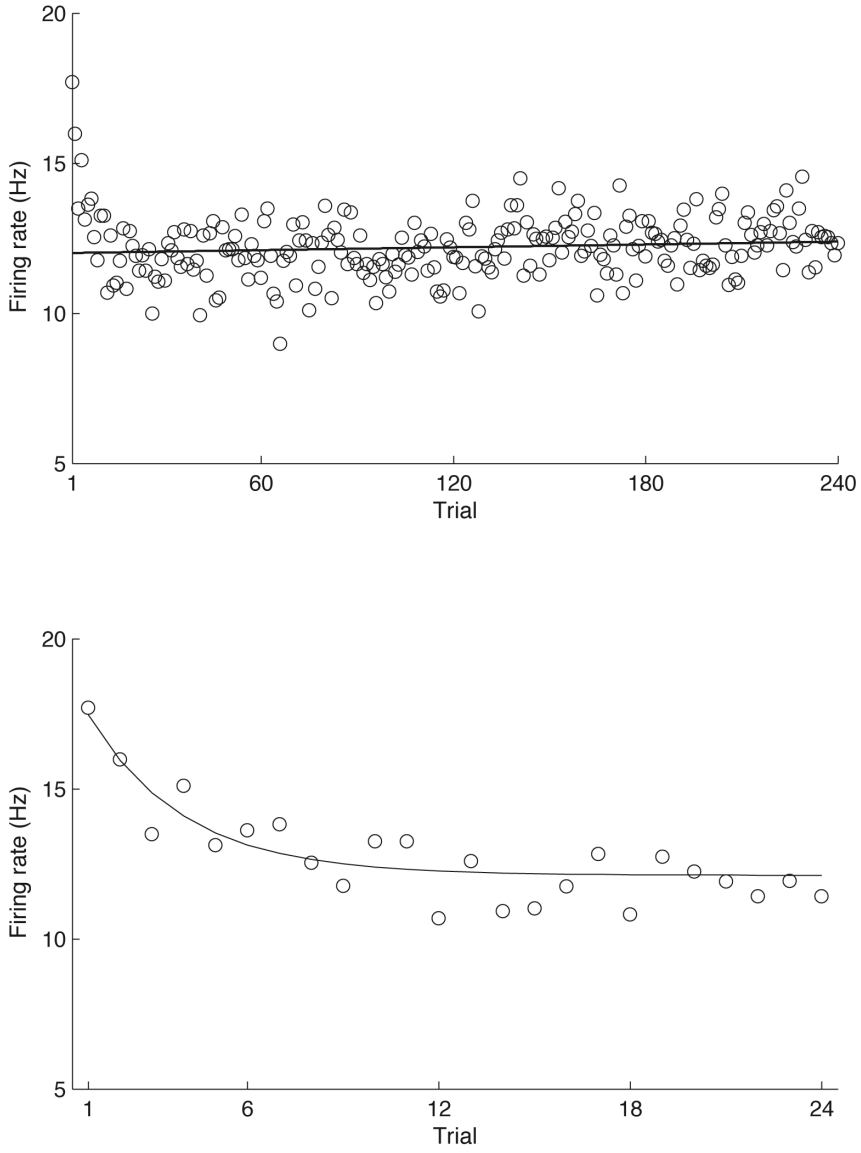


Figure 23. **(A)** Mean neuronal firing rate as a function of trial number within a session. Each point represents the average firing rate over all 152 neurons. Black line: linear regression fit. **(B)** Mean firing rates for the first 24 trials on an expanded time scale. Black line: exponential decay fit.

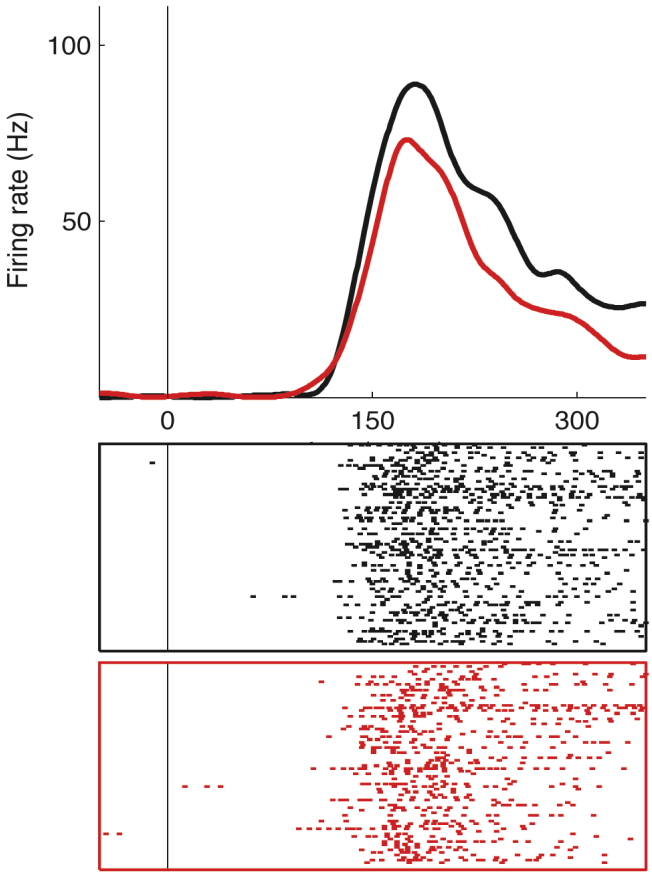


Figure 24. Stimulus repetition induces a reduction in neural activity. Activity of a single IT neuron in monkey EG in response to all visual stimuli in an experimental session, as a function of time. Responses from the first presentation are shown in black, second presentation in red. Top panel shows average responses, and bottom panels show raster data, where each row represents a trial and each point represents a single action potential.

Effects of stimulus repetition on firing rate: repetition suppression.

We monitored the activity of 152 IT neurons (85 and 67 in EG and PH) over the course of the same 118 sessions in which the behavioral data were obtained. An example of the effect of stimulus repetition on one IT neuron is shown in Figure 24. In this neuron, the visual response was clearly suppressed in response to the second stimulus presentation, as is evident from the difference between the two firing rate histograms. How consistent was this effect across the entire population? To answer this question, we assessed repetition suppression as the pair-wise difference in firing rate for each stimulus (FR_1 - FR_2). Only stimuli to which the monkey responded correctly on both presentations were included. Additionally, stimuli that failed to evoke any spikes on either presentation were excluded from analysis. Finally, the first 12 trials of each session were excluded to assure stationary recording conditions, as noted in the preceding section. This filtering procedure yielded 1537-1641 paired neuronal responses at each lag (mean = 1581). The visual response was suppressed on the second presentation of the stimulus in both monkeys (Figure 25 A). The effect was highly significant at lags of 0 and 1 ($p = 1 \cdot 10^{-6}$ and $p = 8 \cdot 1\ 0^{-4}$ respectively, one-sided Wilcoxon signed-rank test) and decreased monotonically as a function of lag, with suppression becoming marginal at lag 8 ($p = 0.04$) and insignificant at lag 16 ($p = 0.34$). The magnitude of suppression at each lag is listed for each monkey and each stimulus type separately in table 3.

To assess the contribution of specific experimental parameters to the suppression effect, we conducted a 3-way ANOVA on FR_1 - FR_2 that modeled the factors **lag**, stimulus **type**, and **monkey**, the results of which are summarized in Table 4. There was a significant main effect of **lag**, which reflected the monotonic trend towards greater suppression at shorter lags. (The effect

of this monotonic trend was such that the suppression effects at lags 0 and 16 were significantly different from each other, Tukey test.) There was also a significant main effect of monkey, which reflected the fact that suppression was greater in monkey PH than in EG (Figure 25A). Contrary to effect of stimulus type on behavioral priming, neuronal suppression was equivalent for symmetrical and asymmetrical stimuli (Figure 25B). None of the interaction effects reached significance. We conclude that neurons in IT undergo repetition suppression under the same circumstances that induce behavioral priming.

Results from a 3-way anova on suppression effects

Source	d.f.	Sum Sq.	Mean Sq.	F-statistic	p-value
lag	5	65.597	13.1194	2.3753	0.0366
type	1	0.0119	0.0119	0.0022	0.963
monkey	1	23.361	23.361	4.2296	0.0397
lag*type	5	29.031	5.8062	1.0512	0.3855
lag*monkey	5	48.9624	9.7925	1.773	0.1147
type*monkey	1	0.5932	0.5932	0.1074	0.7431
lag*type*monkey	5	28.0992	5.6198	1.0175	0.4054
Error	11203	6.19E+04	5.5232		
Total	11226	6.21E+04			

Table 4. Results from a multi-factor ANOVA assessing the effects of three factors on visual response differences between prime and probe stimuli. The three factors were: **lag** (0,1,2,4,8, or 16), stimulus **type** (symmetrical or asymmetrical), and **monkey** (EG or PH).

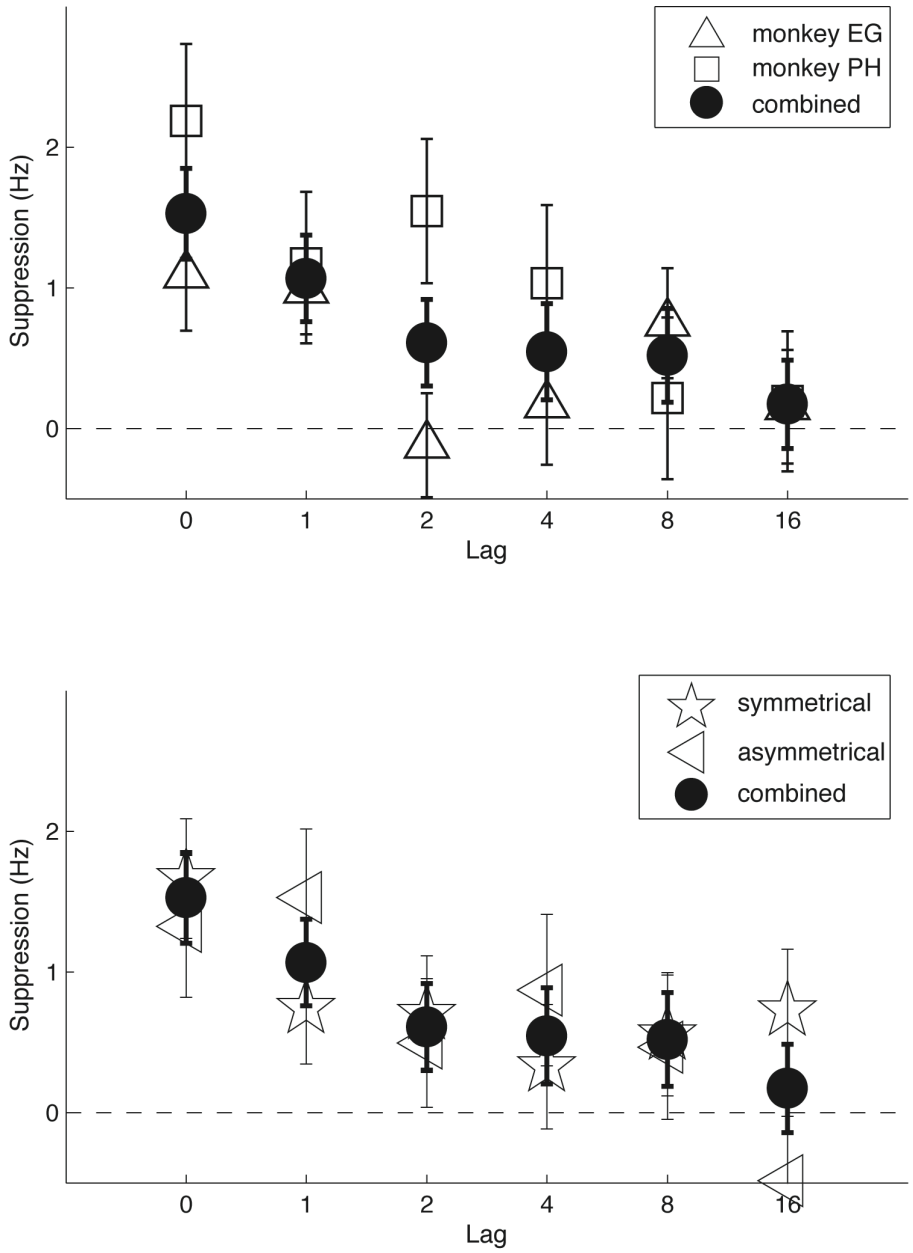


Figure 25. (A) Neuronal suppression as a function of lag, averaged across 152 neurons. Data are shown for monkey EG and PH separately. Suppression was defined as the pair-wise difference in firing rate between first and second presentation of each stimulus (FR_1-FR_2). Stimuli to which the monkey did not respond correctly on both presentations were excluded from analysis. Each point represents the average priming at each lag, based on 1537 to 1641 pairs of stimulus presentations (mean = 1581 stimuli). **(B)** Neuronal suppression for symmetrical and asymmetrical stimuli.

Strength and statistical significance of repetition priming effects

	Lag	Suppression (Hz)	p-value	N pairs
Monkey EG	**0**	1.1	0.0062	928
	1	1.0	0.0143	878
	2	-0.1	0.4749	922
	4	0.2	0.127	869
	8	0.7	0.0385	908
	16	0.2	0.4563	901
Monkey PH	**0**	2.2	4.91E-06	609
	1	1.2	0.0125	677
	2	1.5	0.003	719
	4	1.0	0.0105	678
	8	0.2	0.2756	696
	16	0.2	0.3172	701
Symmetrical	**0**	1.7	3.67E-05	917
	1	0.7	0.0702	911
	2	0.7	0.0705	932
	4	0.3	0.05	921
	8	0.6	0.1525	947
	16	0.7	0.109	868
Asymmetrical	**0**	1.3	0.005	620
	1	1.5	0.001	644
	2	0.5	0.1141	709
	4	0.9	0.0348	626
	8	0.5	0.0752	657
	16	-0.5	0.2324	734

Table 5. Summary of neuronal suppression effects, defined as FR1-FR2. Suppression was statistically significant for 12 out of 24 comparisons ($p < 0.05$, signed-rank tests). Suppression values are given separately for each lag (0 through 16), monkey (EG and PH, collapsed across stimulus type), and stimulus type (symmetrical and asymmetrical, collapsed across monkey).

Latency of neuronal visual responses and of repetition suppression.

The time course of population visual responses is shown in Figure 26. The population response to first presentations is shown in black, and the responses to stimulus repeats at the shortest lags (0, 1, and 2) are shown in red (in order of decreasing line thickness). The latency of the earliest observable suppression effect (i.e., the time at which the black and red curves separate, shown for lag 0 by the white arrow) is clearly delayed relative to the onset of the visual response (black arrow). The latency of suppression for all lags is shown in Figure 27, together with the visual response latency. Repetition suppression at the longer lags (4 and 8) emerged significantly later than suppression at the earlier lags (0,1, and 2) ($p < 0.05$, bootstrap simulation). In contrast, the latency of the visual response was unaffected by stimulus repetition ($p > 0.05$). These observations on timing are concordant with previous results obtained outside the priming paradigm (Li et al 1993, Ringo 1996). The fact that the strength of the earliest phase of the response was identical on first and second presentations allows us to reject the accumulator model, according to which the earliest phase of the response to the second presentation is stronger and net suppression arises only because the response terminates earlier (James and Gauthier, in press, Grill-Spector et al, in press). The fact that suppression developed well after the onset of the initial visual response suggests that repetition-induced changes occur in feedback or lateral pathways, rather than in feed-forward pathways.

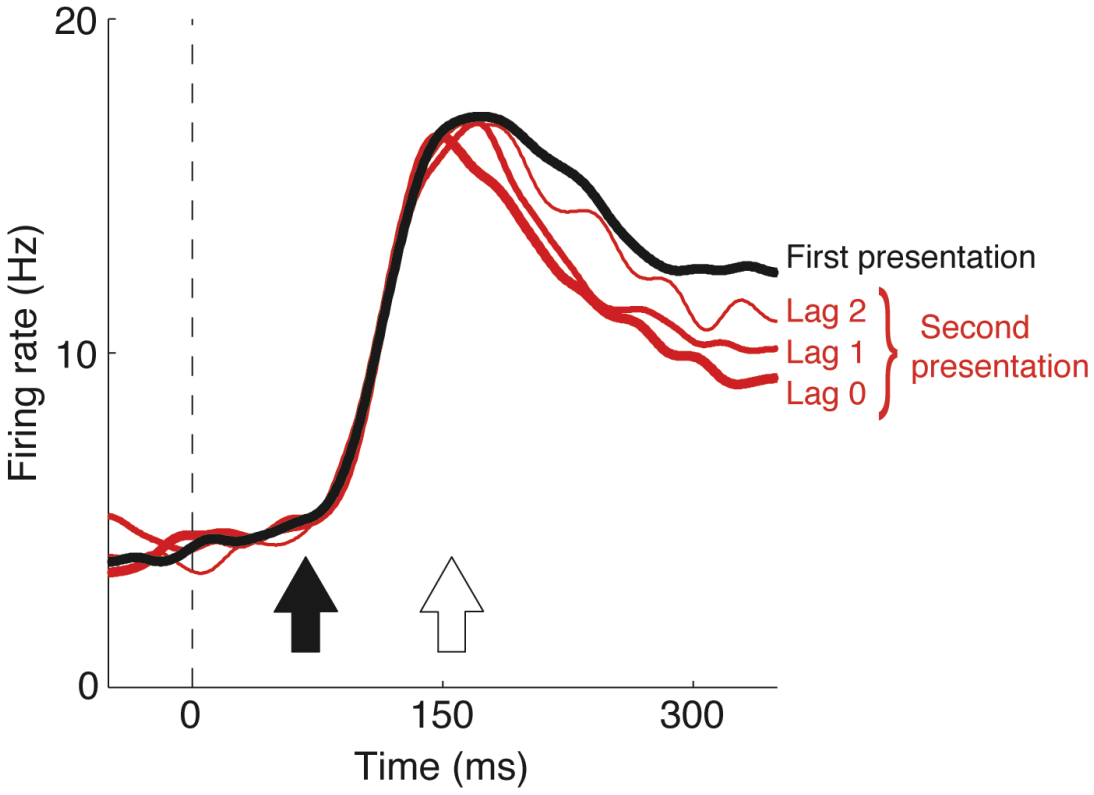


Figure 26. Population histograms of neural firing rate, aligned on stimulus onset. Responses were smoothed by convolution with a 10 ms Gaussian kernel. Black line: first presentation. Red lines: second presentations at lag 0, 1, and 2. Black arrow: latency of population visual response (first presentation). White arrow: latencies of suppression effect (lag 0 repeats).

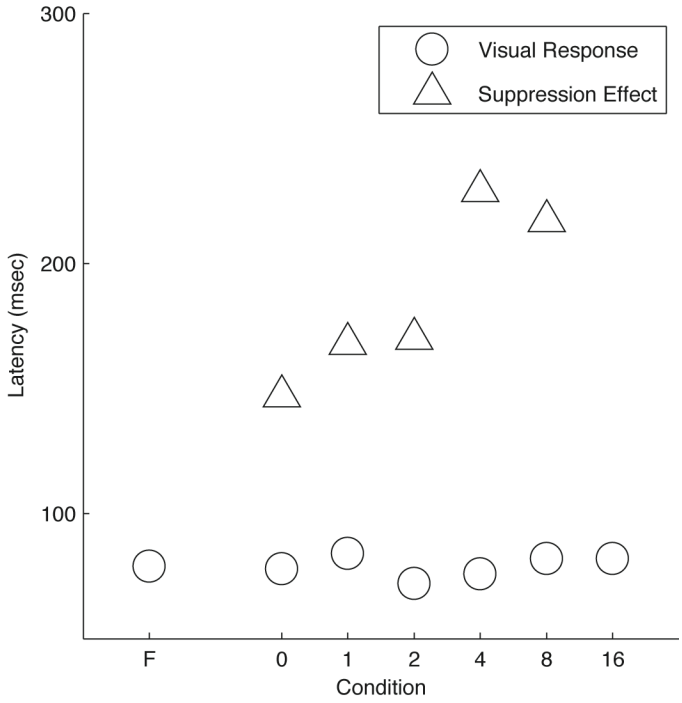


Figure 27 Population summary of the latency values estimated for visual response (circles) and repetition suppression (triangles). Visual response latency was estimated for first presentations pooled together, and for second presentations at all six lags separately. Repetition suppression was not significant at lag 16, therefore latency was not estimated. Suppression was consistently later than initial visual response.

Summary.

In the previous section, we showed that stimulus repetitions facilitate behavioral performance in monkeys performing the symmetry decision task. In this section, we provided the first demonstration that repetition suppression is induced in single IT neurons in the context of a repetition priming task. We showed that visual responses were suppressed by stimulus repeats in a manner that decayed monotonically with increasing lag. Suppression was found to be independent of stimulus type, despite the fact that the magnitude of visual responses were stronger for symmetrical stimuli. Neuronal suppression was delayed relative to the onset of visual response. These results establish for the first time that repetition suppression at the neuronal level accompanies repetition priming at the behavioral level. In the next section, we will consider the relation between behavioral priming and neuronal suppression. In the final section of results, we will assess the effect of repetition suppression on stimulus selectivity.

3.4.3 Comparison between behavioral and physiological effects

In sections 1 and 2 we demonstrated that repetition exerts an effect on both behavioral reaction time and neuronal firing rate. In this section we will ask whether the effects of repetition on behavior and neurons are related, or alternatively whether they co-occur under the same conditions but are independent of each other. The hypothesis that repetition suppression causes repetition priming makes three predictions, which we test in this section. First, trials on which faster RTs occurred (more priming) should be accompanied by lower neuronal firing rates (more suppression). Although the "causality" hypothesis gives rise to this expectation, it is not a logical requirement. Second, the degree of priming and suppression should covary across behavioral sessions. Third, the degree of priming and suppression should covary across individual stimuli. The last prediction is in fact a logical requirement of the hypothesis.

Comparison between firing rate and reaction time across trials.

In the preceding section we demonstrated that repetition suppression at the level of single neurons in IT accompanies repetition priming at the level of behavior. It does not necessarily follow, however, that the observed neuronal effect is directly attributable to stimulus repetition per se. The possibility exists that fast behavioral RTs happen to coincide with low firing rates irrespective of stimulus repetition. If this were the case, the suppression effects that we attributed to repetition would in fact be a consequence of faster RTs. In order to dissociate the contributions of behavioral RT and presentation order (first or second), we divided the range of behavioral RTs into three equal quantiles. We then conducted a 2-way ANOVA that assessed the effects of **RT quantile** (fast, medum, or slow) and **repetition** status (first or second). There were significant main effects of both factors, but no significant interaction effects. Contrary to

the idea that low rates of firing are associated with fast responses, the opposite result accounted for the main effect of **RT quantile** ((p = 0.005; Figure 28A). In other words, we found that firing rates were in fact highest on average for the fastest RTs. The same monotonic trend in the population was reproduced in monkey EG ($p = 5 \cdot 10^{-9}$; Figure 28B). The RT quantile main effect was also significant for monkey PH (p = 0.02), although in this case the trend was non-monotonic, (Figure 28C). There was also a significant main effect of **repetition** (p = 0.0001), which was also significant in both monkeys (p = 0.03 and p = 0.002 in EG and PH respectively). Taken together, these results establish that neuronal suppression does not arise from RT variance independent of stimulus repetition, but rather is a consequence of stimulus repetition per se.

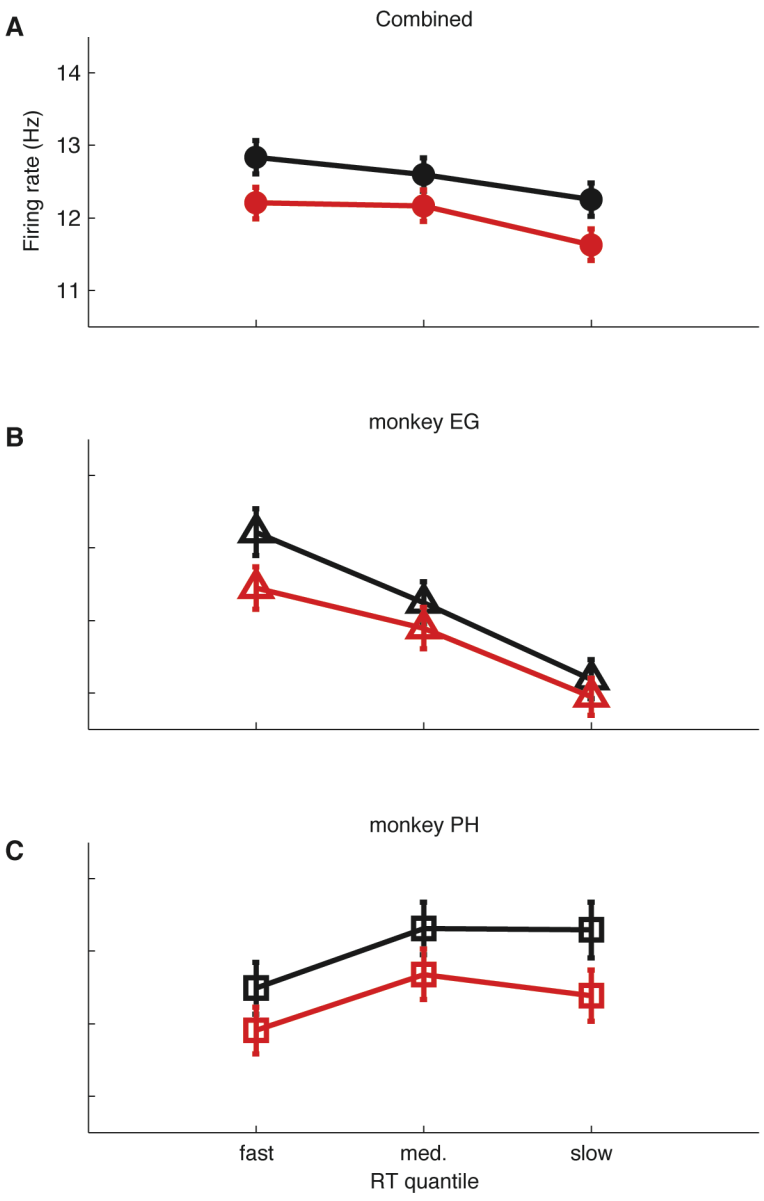


Figure 28. On average, neural activity (y axis) is smallest when reaction time (x axis) is slowest. Reaction-time data are divided into three quantiles constituting fast (RT < 290 ms), medium, and slow (RT > 345 ms). Black symbols represent average firing rates for first presentations, red symbols represent those for second presentations. Data are shown for the two monkeys combined **(A)** and for each individual monkey **(B, C)**.

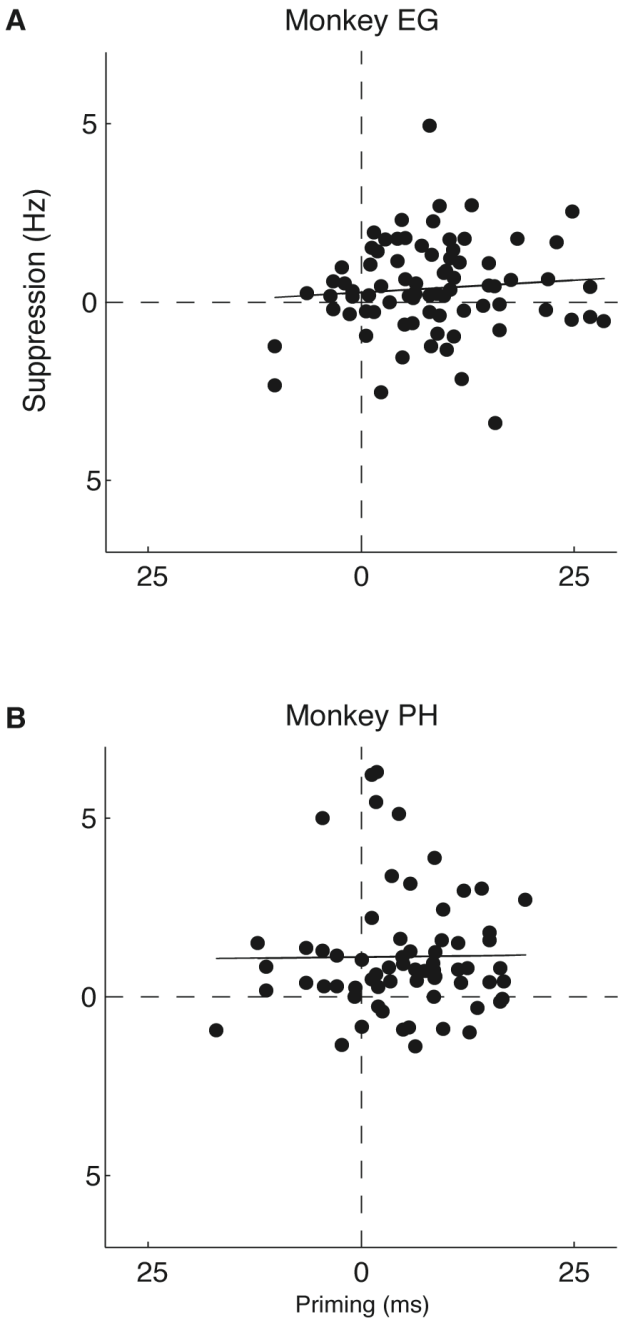


Figure 29. Repetition priming and repetition suppression do not co-vary across sessions. Data are shown separately for monkey EG **(A)** and monkey PH **(B)**. Scatterplots show the relationship between the behavioral effects of stimulus repetition (mean of RT_1 - RT_2 over all stimuli, x axis) and the neural effects of repetition (mean of FR_1 - FR_2 over all stimuli, y axis). Each point represents data from a single experimental session. For both monkeys (shown separately), there is no significant relationship between the average strength of behavioral priming and the average strength of neural suppression across recording sessions. Lines show the best linear regression fit.

Comparison between priming and suppression.

In the preceding section we determined that fast behavioral RTs are not associated with low neuronal firing rates. While such a relation might be inferred from the general hypothesis that repetition suppression and repetition priming are causally related, it is not a necessary requirement of the hypothesis. A stronger prediction is that the magnitude of *repetition-induced changes* in RT and firing rate should be correlated, as distinct from a relation between RT and firing rate on a given trial. We tested this prediction in two ways. First, we asked whether the mean levels of priming and suppression effects covaried across experimental sessions (Figure 29). There was no significant correlation in either monkey (monkey EG: $r = 0.087$, $p = 0.44$; monkey PH: $r = 0.012$, $p = 0.92$). This result is consistent with the failure in several human imaging studies to detect a consistent positive cross-subject correlation between behavioral priming and BOLD signal reductions in visual cortex (Maccotta and Buckner 2004, Dobbins et al 2004, Sayres and Grill-Spector 2003, Wig et al 2005). Second, we conducted a correlation analysis between priming and suppression across all pairs of trials in which the monkey responded correctly to both presentations of a stimulus. This analysis was performed separately for 24 conditions (two monkeys, two stimulus types, and six lags). The results from the four lag 0 conditions (both monkeys, symmetrical and asymmetrical stimuli) is shown in Figure 30. Because repeats at lag 0 had the greatest impact on both behavior and neural activity, these conditions have the greatest chance of revealing a correlation. In fact, priming and repetition suppression were uncorrelated in all four cases. The same result was observed for all the longer lags as well: there was no case of a significant positive correlation in any of the 24 conditions tested (Table 6), nor was there a significant correlation in data pooled from all the conditions.

The rationale for splitting the data pool by monkey and stimulus types was to avoid spurious correlations that might be introduced by differences between EG and PH, or between responses to symmetrical and asymmetrical stimuli. The rationale for examining each lag separately was to determine whether any lag-specific correlation effects were observable. Conducting the same analysis on the entire data set pooled together also did not result in a significant correlation.

Theoretically, the hypothesis that repetition suppression is the neural basis of repetition priming requires a correlation between the two. However, the experimental finding that these measures of suppression and priming are uncorrelated does not rule out the existence of a causal relation between the two, because cross-session or cross-trial variance in the two measures could have derived from independent sources of variability outside the processes of suppression and priming themselves. Nonetheless, further studies will clearly be necessary to settle the question of whether a causal relation exists between priming and neuronal suppression.

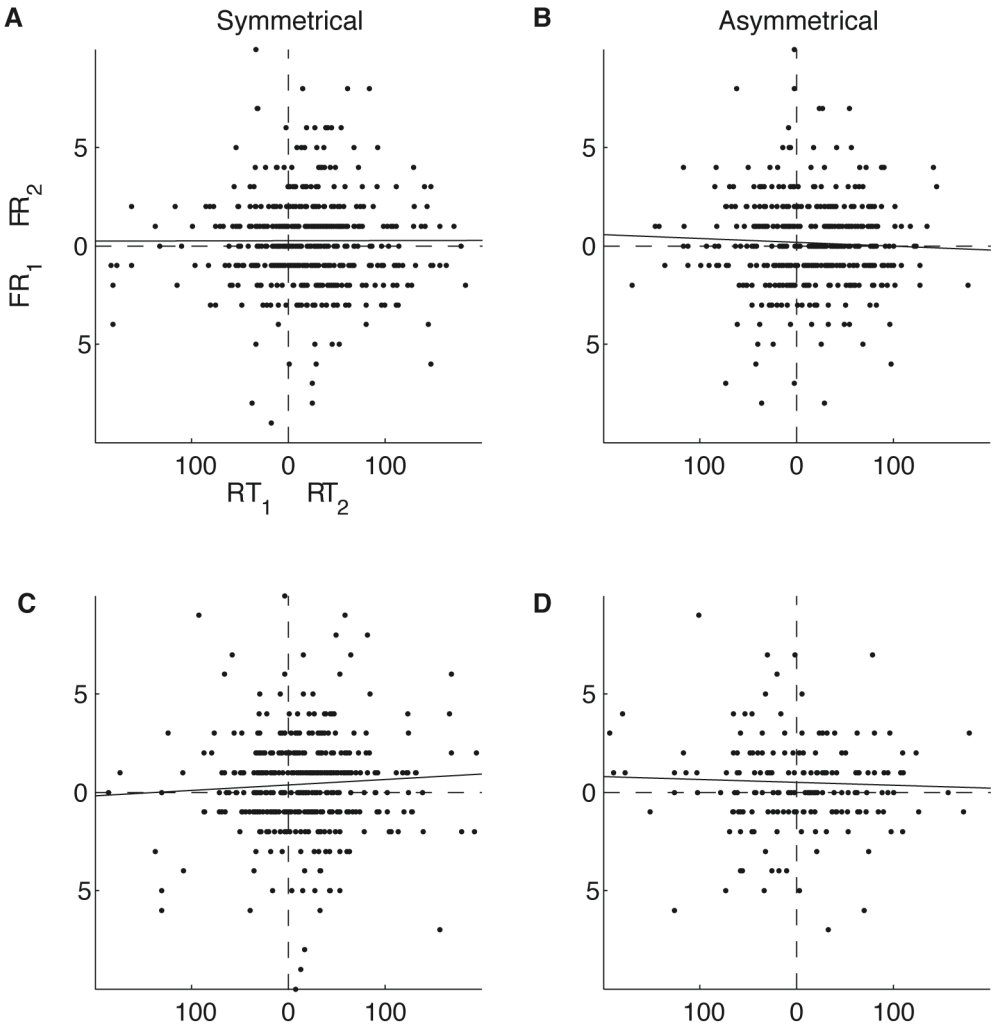


Figure 30. Results from linear regression analyses for lag 0 stimulus repeats. Each data point represents a single stimulus. Each plot assesses the degree of correlation between behavioral priming (RT_1 - RT_2) and neuronal suppression (FR_1 - FR_2). Data are segregated for monkey EG (shown in panels **A** and **B**) and monkey PH (panels C and D), and by symmetrical (panels **A** and **C**) and asymmetrical stimuli (panels B and D). The correlation was computed over the set of all stimuli to which the subject responded correctly on both presentations.

Analysis of correlation between priming and suppression

		Lag	R coefficient	p value	N stimuli
Monkey EG	Symmetrical	0	0.012	0.80	494
		1	0.018	0.69	477
		2	0.034	0.46	486
		4	0.054	0.25	468
		8	0.078	0.08	497
		16	- 0.029	0.55	438
	Asymmetrical	0	- 0.077	0.11	434
		1	- 0.126	0.01	401
		2	- 0.045	0.35	436
		4	- 0.016	0.74	401
		8	0.020	0.69	411
		16	0.015	0.74	463
Monkey PH	Symmetrical	0	0.032	0.51	423
		1	0.066	0.17	434
		2	0.026	0.58	446
		4	0.047	0.32	453
		8	0.043	0.36	450
		16	- 0.052	0.28	430
	Asymmetrical	0	0.051	0.49	186
		1	- 0.041	0.53	243
		2	- 0.159	0.01	273
		4	- 0.064	0.34	225
		8	- 0.007	0.99	246
		16	0.064	0.30	271

Table 6. Results of 24 separate linear regression analyses assessing the degree of correlation between behavioral priming and neuronal suppression. The correlation was computed over the set of all stimuli to which the subject responded correctly on both presentations. Priming was defined as (RT_1 - RT_2) and repetition suppression was defined as (FR_1 - FR_2), where RT_1 and RT_2 were the reaction times and FR_1 and FR_2 were the firing rates on first- and second-presentation trials.

Summary.

The assumption that behavioral priming and neuronal suppression are causally related gives rise to several expectations. In this section, we evaluated the relation between the behavior and neural activity. If low neuronal firing rates tend to co-occur with fast reaction times, then repetition suppression might be due to the variance in RT across sessions, rather than to stimulus repetition per se. In fact, we demonstrated that trials with faster RTs are not associated with lower firing rates; rather, the opposite trend prevailed. We further demonstrated that repetition suppression was not correlated with repetition priming, whether assessed across neurons or across stimuli. These negative findings could reflect a genuine lack of an underlying correlation between the observed changes in behavioral and neuronal responses. However, they could also simply reflect the limits of sensitivity afforded by our particular experimental conditions. The interpretation of these findings will be considered further in chapter 4.

3.3.4 Effect of repetition on stimulus selectivity

In the preceding section, we demonstrated that repetition suppression and repetition priming do not covary, at least to an extent that is detectable under our experimental conditions. However, we cannot conclude on the basis of that negative result that priming and suppression are unrelated. In the current section, we evaluate the predictions of two models of how repetition suppression affects stimulus selectivity. The sharpening model predicts that stimulus selectivity is enhanced by stimulus repetition. In contrast, the scaling hypothesis predicts that the magnitude of neuronal responses is uniformly reduced by stimulus repetition, and thus selectivity is unaffected. The predictions of the two models are mutually contradictory, and constrain the possibilities for a causal relation between priming and suppression. Before considering the effect of suppression on stimulus selectivity, we first establish that selectivity is reliably measured under our experimental conditions.

Test-retest reliability of neural selectivity.

In eliciting behavioral priming, we necessarily employed a large set of stimuli chosen without respect to the individual neuron's preferences (pre-testing the stimuli would have compromised their efficacy as primes and probes). Furthermore, each stimulus was presented only twice (as required for demonstrating priming). It might be questioned whether the neurons were commonly selective for the stimuli and whether, if they were selective, we could demonstrate their selectivity using so few presentations. To address these issues, we conducted a linear regression analysis on the visual responses evoked by first and second presentations across all cases in which the monkey responded correctly to both presentations. An example is shown in Figure 31A. For this cell, the relation between the firing rates on the first and second

presentations was highly significant (N = 78 stimuli, R = 0.66, $p = 3.5 \cdot 10^{-11}$). The correlation coefficient was positive in 95% (144/152) of all neurons and achieved significance in 63% (90/144) (Figure 31B). Thus IT neurons did respond selectively even though the stimuli were chosen arbitrarily, and their selectivity was demonstrable even though each stimulus was presented only twice. In light of this finding that stimulus selectivity is measurable on the basis of a single presentation per stimulus, it is feasible to consider whether repetition induces changes in selectivity.

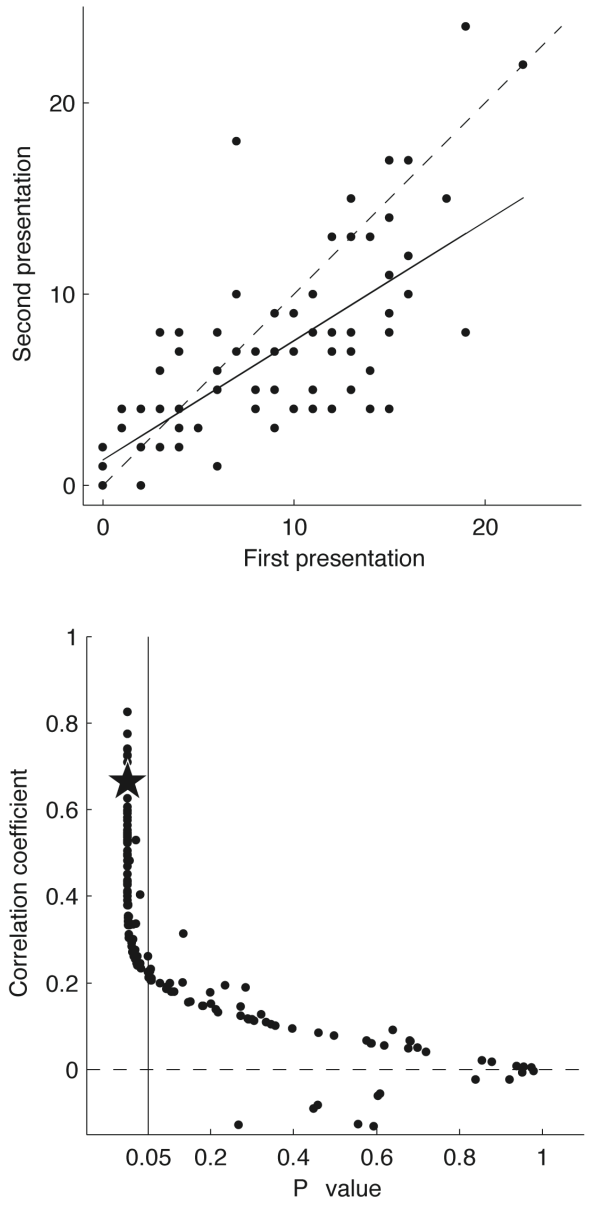


Figure 31. (A) Selectivity of single neurons is consistent across initial and repeated presentations. Correlation between spikes from a single neuron (from monkey EG) on first and second presentation of 78 different stimuli. R = 0.66, $p = 3 \cdot 10^{-11}$. **(B)** The majority of IT neurons had similar selectivity for first and second presentations of the same stimulus. Each point represents a single neuron (n=152). Star indicates the cell shown in panel A. The y axis shows the R value representing the strength of similarity between firing rates in response to first and second presentations; x axis shows the corresponding p value. There was a positive correlation in 144 out of 152 neurons, which reached statistical significance in 90 neurons ($p < 0.05$, indicated by vertical line).

Contrasting models of repetition suppression: Sharpening or scaling?

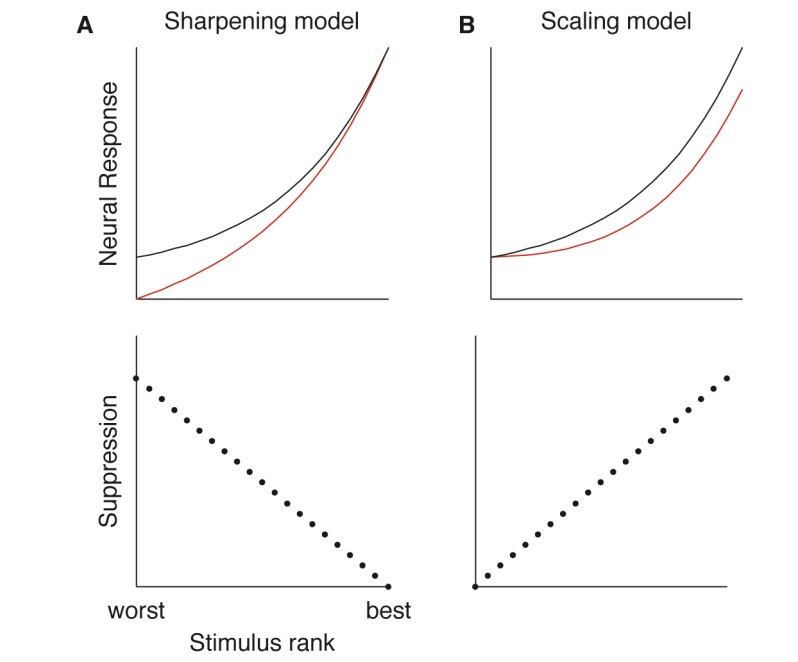
Two alternative hypotheses have been proposed with regards to the effect of repetition suppression on stimulus selectivity in IT neurons. Both hypotheses are illustrated by the tuning curves of hypothetical neurons shown in Figure 32A. According to the sharpening hypothesis, the degree of suppression is proportionally greater for stimuli that elicit a weak response from a given neuron than for stimuli that elicit a strong response (Ungerleider 1995, Desimone 1996, Wiggs and Martin 1998, Grill-Spector et al 2005). The sharpening model predicts that stimulus selectivity is enhanced upon repetition (Figure 32A). In contrast, according to the scaling hypothesis the degree of suppression is a constant proportion of the initial response regardless of stimulus efficacy (Li et al 1993, Avidan et al 2002, Grill-Spector et al 2005). The scaling model predicts that stimulus selectivity is unaffected by repetition (Figure 32B).

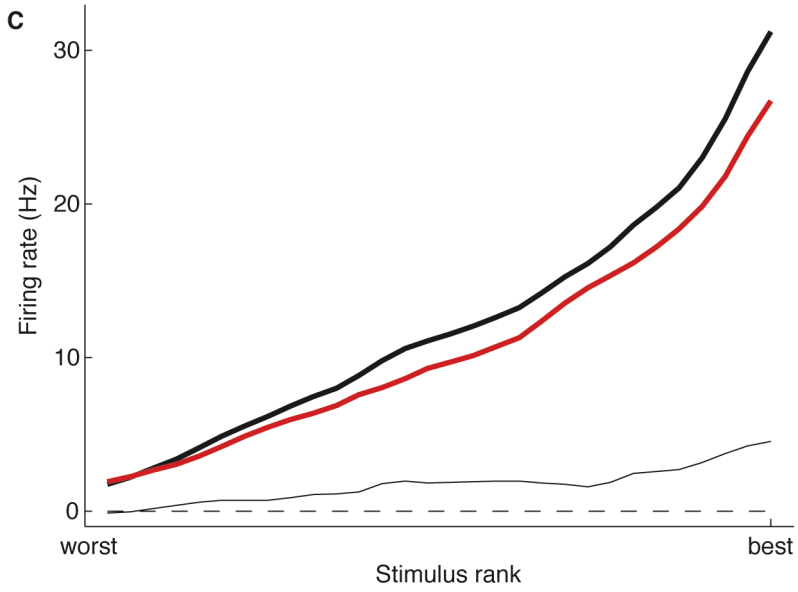
Scaling of the IT population tuning curve.

In order to directly visualize the effect of repetition suppression on stimulus selectivity in IT, we constructed a selectivity profile for each neuron representing response strength as a function of stimulus rank (from the least effective to the most effective stimulus) for first and second presentations. Then, averaging across neurons, we constructed population selectivity profiles (Figure 32C). The profiles from the first and second presentations appear closely similar in shape. In fact, they were not significantly different when normalized to eliminate the overall reduction in firing rate resulting from response suppression ($p = 0.94$, Kolmogorov-Smirnov test). Thus, upon repetition, the sharpness of neuronal tuning for images in the stimulus set was unaltered.

Because repetition at short lags caused the strongest suppression, we assessed the effect of repetition suppression on stimulus selectivity by focusing on stimuli that were repeated at lags 0 and 1. On the basis of the finding that suppression emerged after 150 ms, (Figure 26), neuronal firing rates were measured over a 150 to 350 ms time window. Exploratory analysis based on all lags (0 through 16) or an earlier integration window (80 to 280 ms) confirmed that our conclusions do not depend on any particular set of filtering procedures.

Figure 32 (overleaf). Alternative models of repetition suppression: **(A)** Sharpening, vs. **(B)** Scaling. The upper plots illustrate the tuning profile of two hypothetical neurons before and after stimulus repetition (black and red lines). The lower plots show the difference between the pair of tuning curves shown above (black minus red) plotted with an expanded y-axis. The sharpening model predicts that repetition induces little or no suppression for the most effective stimulus. In contrast, the scaling model predicts that suppression is a constant proportion of the original stimulus efficacy. **(C)** Effect of repetition suppression on neural selectivity. The thick lines reflect the average population response for 152 neurons, plotted against relative stimulus rank (black: first presentation, red: second presentation). The thin line is the difference between the two solid lines. Tuning curves for each neuron were constructed by sorting responses into 30 bins ranging from worst to best. Uniform binning was necessary to allow for averaging across a set of 152 tuning curves that were derived from different numbers of effective visual responses.


A
Sharpening model
B
Scaling model
Neural Response
Suppression
worst
best
Stimulus rank


C
30
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Firing rate (Hz)
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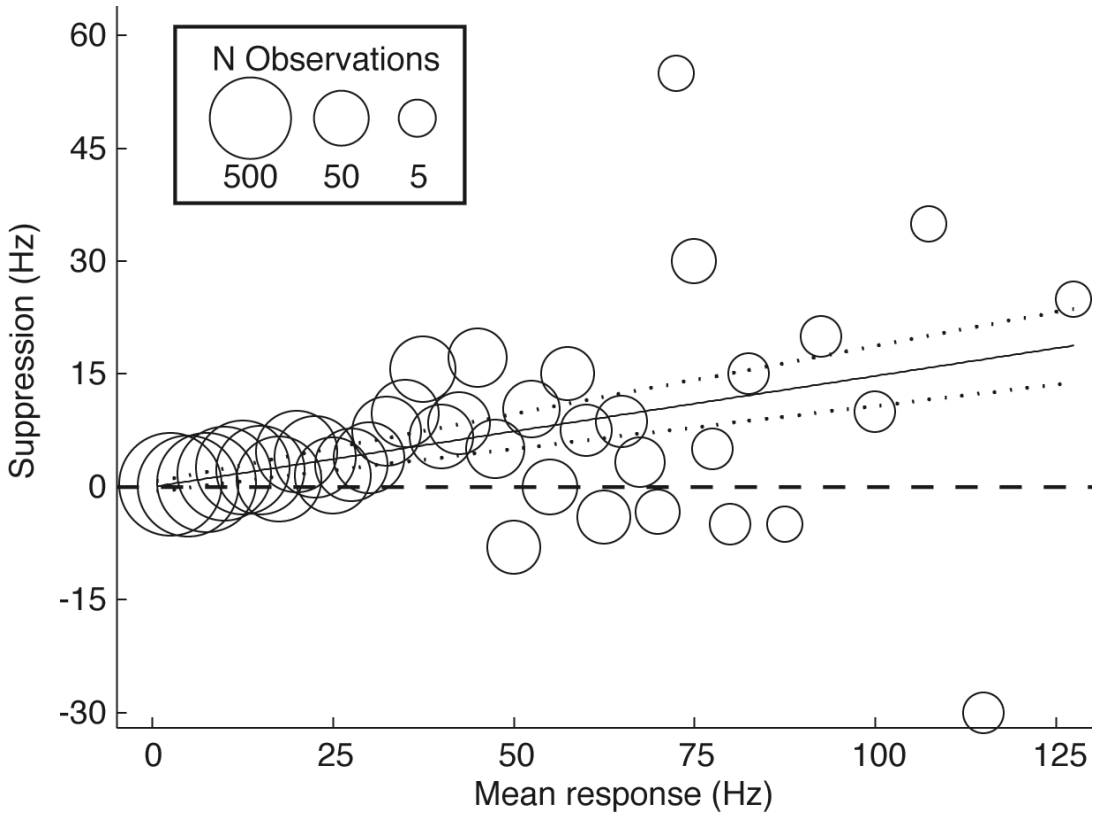


Figure 33. Relation between suppression and mean response strength across all pairs of stimuli repeated at lag 0 or lag 1 (N = 3028 paired stimulus presentations). Suppression in spikes per second (FR_1 - FR_2) is plotted against mean response strength [(FR_1 + FR_2)/2]. Values along the x-axis fall into discrete bins of 2.5 Hz because they are the average of two spike-counts within a 200 ms window (150-350 ms after stimulus onset). For the sake of clarity only the mean suppression at each bin is shown. The size of each circle is proportional to the square root of the number of observations within the corresponding bins. The regression line and 95% confidence intervals (black and dotted lines) represent a linear fit to all 3028 stimulus pairs. The significant positive correlation ($R = 0.16$, $p < 10^{-10}$). indicates that repetition suppression scales linearly with the magnitude of visual response.

The preceding analysis examined the effect of stimulus efficacy and repetition suppression on the basis of stimulus ranking relative to each neuron's selectivity profile. We also assessed the relation between absolute firing rate and repetition suppression. Figure 33 shows the scatter-plot of suppression (FR_1 - FR_2) plotted against mean response strength [(FR_1 + FR_2)/2], using the same filtering procedure described above. The results show clearly that repetition suppression is proportional to mean response strength ($p < 10^{-10}$, $R = 0.16$). Stimulus repetition had the effect of reducing the strength of the original response by 14.7% on average (11.4% - 18.1%, upper and lower 95% confidence intervals). We conclude that repetition suppression reduces visual responses in IT via a linear scaling mechanism, rather than via a sharpening mechanism.

Summary.

In this section, we tested the predictions of the sharpening and the scaling models on stimulus selectivity in IT neurons. Stimulus selectivity was shown to be reliably estimated on the basis of a single observation per stimulus. We demonstrated that repetition suppression is proportional to stimulus selectivity in IT. Visual responses were proportionally scaled by a factor of approximately 15% for stimulus repeats at lags of 0 and 1. We conclude that, if repetition suppression contributes to behavioral priming, it must do so by some mechanism other than sharpening. In the next section, we shall consider how priming might be consistent with scaling of visual responses.

3.5. Discussion

3.5.1 Comparison to previous studies of repetition suppression

The results presented in this chapter constitute the first demonstration that repetition suppression at the neuronal level accompanies repetition priming at the behavioral level. Our results are broadly consistent with the findings that neuronal suppression is stimulus specific (Li et al 1993, Fahy et al 1993, Sobotka 1996), decays gradually and persists over multiple intervening stimulus presentations (Miller et al 1991, Li et al 1993, Fahy et al 1993), and does not depend on tasks requiring explicit memory of the repeated stimulus (Li et al 1993, Miller and Desimone 1994). Previous studies have demonstrated that repetition suppression in IT occurs in the context of explicit memory tasks (Baylis and Rolls 1987, Riches et al 1991, Fahy et al 1993, Sobotka and Ringo 1993), which initially led to the suggestion that neuronal suppression might mediate successful performance on such tasks. However, the generality of this interpretation was undermined by demonstrations that neuronal suppression also results from stimulus repetition during passive visual fixation, when a behavioral response is not required (Miller et al 1991, Sary et al 1995), and under conditions when a behavioral response is specifically counter-indicated (Miller and Desimone 1994).

More recent proposals have linked repetition suppression to priming because of the temporal characteristics of repetition suppression (rapid induction, rapid initial decay, and residual

persistence, all of which are similar to priming effects), in addition to its dissociation from explicit recall (Wiggs and Martin 1998). What is the origin of repetition suppression in IT? One way to address this question is to consider the timing of neural activity associated with repeated stimulus exposure. We found that the firing rate differences between the first and second presentations were delayed relative to the latency of visual response (figure 26). The latency of the neuronal suppression we observed in our study is in agreement with the latency estimates obtained in earlier studies (Li et al 1993, Sobotka 1996). This delay between visual response latency (80 ms) and suppression latency (149 ms) argues against the interpretation that repetition suppression is inherited from adaptation effects in earlier visual areas (e.g., Kohn and Movshon 2003). A more likely scenario is that repetition suppression emerges either from lateral connections within IT itself, or is imposed by feedback projections from higher level association areas. It has recently been proposed that stimulus-induced reductions BOLD signal reductions might be due to an initial increase in the rate of spike accumulation in IT, followed by an earlier decay of firing rate (James and Gauthier, in press, Grill-Spector et al, in press). The reasoning behind this idea, known as the "accumulator" model, is that neuronal processing in IT persists until the network settles into a representational state that accounts for the sensory input arriving from earlier visual areas. Once a consistent interpretation of the sensory data emerges, further processing is truncated and activity decays in the network's units (i.e., single neurons in IT). In our data, we did not find any evidence supporting this model, thus it is unlikely that IT instantiates an accumulator as proposed by James and Gauthier. However, the possibility exists that suppression in IT might be mediated by feedback projections from a higher-order area that might act as an accumulator.

A central unresolved issue has been the relation between the strength of repetition suppression and that of the initial visual response. Li et al (1993) reported that neurons which undergo a statistically significant degree of repetition suppression have higher initial firing rates than neurons with insignificant effects. This finding suggests that the magnitude of repetition suppression increases monotonically with stimulus efficacy, although the authors did not assess this relation directly. This property of repetition suppression is of critical interest in the interpretation of BOLD signal reductions in terms of the response properties of single neurons (Grill-Spector and Malach 2001, Avidan et al 2002). However, the association between strong suppression and strong visual responses reported by Li et al was confounded by the use of novel stimuli as sample and matching objects, and the use of familiar stimuli as non-matching probes. Relative to familiar images, novel stimuli are known to be both more effective at evoking visual responses in IT neurons, and also more effective at inducing repetition suppression IT (Li et al 1993, Fahy et al 1993, Xiang and Brown 1998). Thus, the data from Li et al do not establish that repetition suppression in IT follows a scaling rule. The results presented in the current chapter are the first demonstration that repetition suppression scales linearly with magnitude of visual response when the confounding influence of novelty is eliminated.

3.5.2 On the potential relation of repetition suppression to behavioral priming

The hypothesis that repetition suppression is the neural mechanism for repetition priming is one that is widely held in the field (Schacter and Buckner 1998, Wiggs and Martin 1998, Henson 2003, Grill-Spector at al 2005). In our study, we found that the magnitudes of priming and suppression were uncorrelated, whether we assessed the relation across sessions (Figure 29) or across stimuli (Figure 30). At minimum, this result calls into question whether a causal relation could exist between the two. However, although the causality proposition logically requires that the degree of priming be correlated with neural suppression, nothing requires that such a correlation actually be detectable under any given set of experimental conditions. This negative result must be interpreted judiciously, in light of the fact that both behavioral RTs and neuronal firing rates are highly variable processes, and might be subject to independent sources of noise.

Our results indicate that the proposed mechanism whereby repetition suppression facilitates priming needs to be reconsidered. The sharpening model was initially proposed to account for the paradoxical finding that faster behavioral responses are accompanied by reduced activity in the same cortical areas that are presumably mediating the primed behavior. Our results demonstrate that selectivity undergoes proportional scaling, rather than sharpening, and thus sharpening cannot mediate repetition priming. The scaling model of repetition suppression stands in contrast to models of longer lasting plasticity in the visual system. There is evidence that sharpening plays a role in long-term expertise effects that result from sustained training periods in monkeys (Rainer and Miller 2000, Baker et al 2002). At least as far as repetition priming over short intervals is concerned, our findings establish that sharpening does not occur in IT neurons.

It remains to be determined whether a scaling effect could contribute to faster behavioral responses. One possibility is that some subsequent processing stage interprets activity in IT by sorting responses in IT into binary levels by applying a criterion threshold. According to this scenario, activity in a particular neuron is regarded as either supporting the hypothesis that a particular object is present within the cell's receptive field, or it is not. After suppression, a neuron's activity would only be construed as evidence in favor of a very small number of stimuli, namely the items which were most effective at driving the cell. However, it is not clear how robust such a mechanism would be to noise. An alternative mechanism has recently been proposed by Gotts (2003). The logic of this model is as follows: Populations of spiking neurons synchronize more readily if the distributions of firing rates is homogeneous. Repetition suppression reduces the range of firing rates, and facilitates synchronous spiking. Synchronous firing among IT neurons increase the probability of spike transmission to their downstream targets. Under certain conditions, the firing rate reduction is more than compensated for by the increased efficacy of each spike due to synchrony. This proposal is attractive in that it reconciles the apparent discrepancy between the observation that repetition suppression exerts a scaling effect on neural responses. Confirmation of this hypothesis must await physiological recordings with multiple simultaneous electrodes, so that the effects of stimulus repetition on synchrony can be assessed.

3.5.3 Possible cellular mechanisms of repetition suppression

For reasons of practicality, most of our knowledge about the biophysical processes mediating short-term plasticity in the visual system come from intracellular recording studies of neurons in

cat striate cortex, rather than from monkey IT cortex. As we discussed earlier, contrast adaptation to prolonged conditioning stimuli is due to Ca^{++} dependent K^{+} currents (Carandini and Ferster 1997). This effect persists for 12-75 seconds, which is consistent with time-course of the repetition suppression effects we observed in IT. Indeed, one computational modeling study simulated repetition suppression effects over brief intervals by including a muscarinic-sensitive K^{+} current in a network of spiking neurons (Sohal and Hasselmo, 2000). The role of cholinergic modulation in repetition suppression is suggested by the fact that physiostigmine (a muscarinic acetylcholine receptor agonist) enhances MR adaptation in LO (Bentley et al 2003). Conversely, stimulus repetition actually induces increases BOLD signal after administration of scopolamine (a muscarinic antagonist, Thiel et al 2001). Taken together, these results indicate that repetition suppression might be mediated by intrinsic membrane properties that are subject to cholinergic modulation.

One problem with the hypothesis that repetition suppression is mediated by intrinsic membrane properties is the discrepancy in time-course between the two. The induction time-constant of visually induced after-hyperpolarization currents in V1 neurons is on the order of 10 seconds (Sanchez-Vives et al 2000b). Repetition suppression in IT is observable much sooner than this. Similarly, contrast adaptation effects induced by briefly presented grating patterns are known to decay with a time constant of 6 seconds, and therefore they cannot be accounted for by after-hyperpolarization currents (Muller et al 1999). An alternative proposal is that short-term synaptic plasticity can account for contrast adaptation over a broad range of time-scales (Abbott et al 1997). This explanation depends on the fact that EPSPs impinging onto V1 neurons undergo strong paired-pulse depression. This effect appears to be presynaptic (Nelson 1991a,

Valera et al 1997), and is consistent with the effect of visual stimulation on spiking neurons (Nelson 1991b). Presynaptic depression is a plausible candidate for repetition suppression in IT, although it is not known whether synapses in IT undergo paired-pulse depression or facilitation. Given the fact that short-term plasticity effects often differ greatly according to brain region (Salin et al 1996, McNaughton 1980), a characterization of paired-pulse effects in slices of monkey TE and perirhinal cortex would be necessary to resolve this question.

3.5.4 Relevance of the cellular mechanisms of suppression in single neurons to MR adaptation

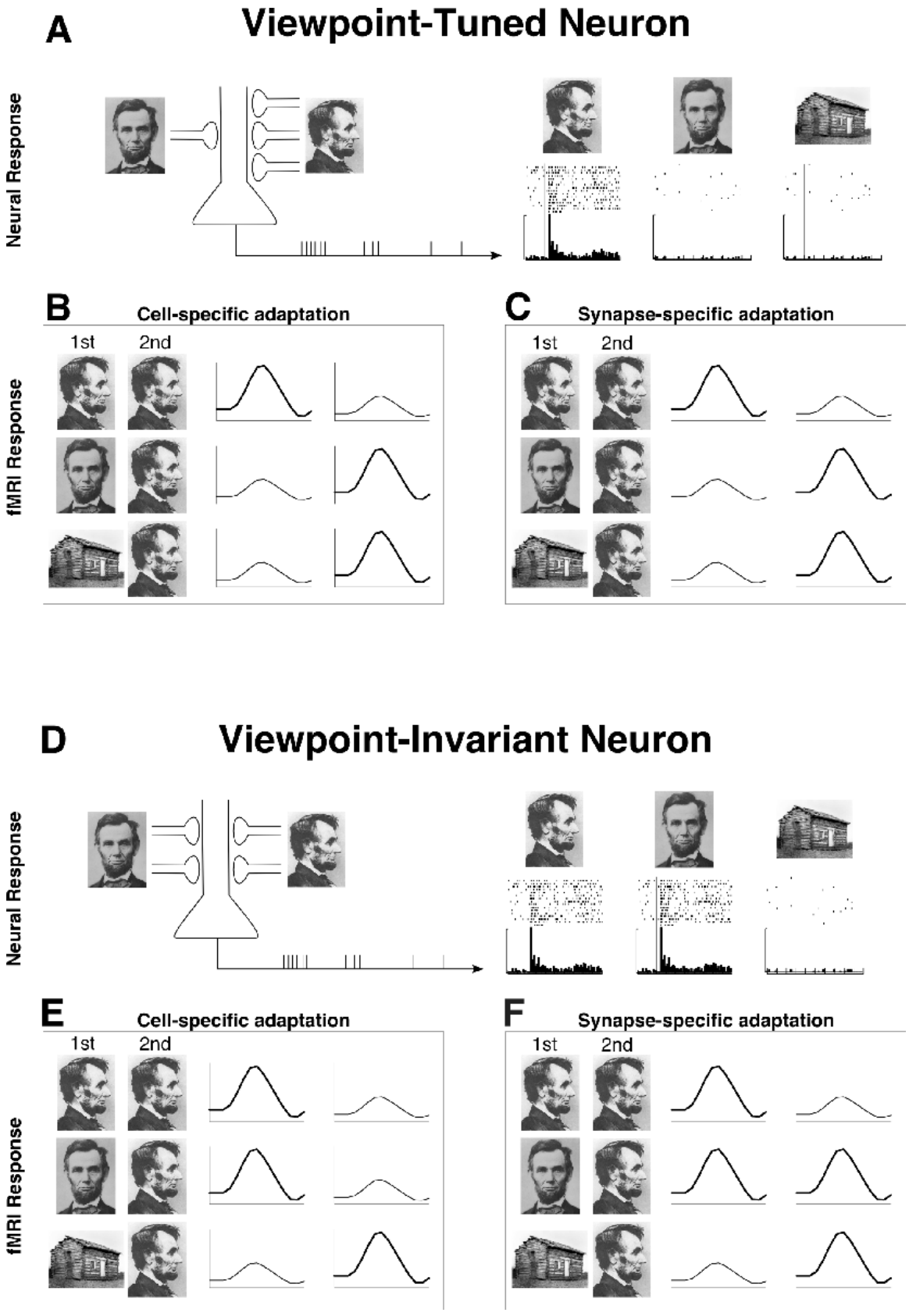
A great deal of the interest in repetition suppression is due to the recent development of MR adaptation as a tool for drawing inferences about the response properties of single neurons (Grill-Spector and Malach, 2001). In recent years, several properties have been attributed to visual representations in LO, which are typically consistent with physiological recording results from IT. In particular, both adaptation effects in human LO and neuronal responses in monkey IT are insensitive to transformations of stimulus location (Grill-Spector et al 1999, Gross et al 1972), size (Sawamura et al 2005, Ito et al 1995), depth rotation (Logothetis et al 1995), and figure-ground organization (Kourtzi and Kanwisher 2001, Baylis and Driver 2001). This pattern of results establishes the general feasibility of the MR adaptation approach, and motivates further consideration of the cellular mechanisms underlying adaptation effects for the purpose of achieving a better understanding of the advantages and limitations of this promising new technique.

The interpretation of MR adaptation effects in terms of single-unit response properties depends on two critical assumptions. The first requirement is that the magnitude of repetition suppression in single neurons increases monotonically with the magnitude of the visual response. This assumption is consistent with the observation by Li et al (1993) that novel stimuli were more effective than familiar stimuli, both in driving IT neurons upon initial presentation, and in inducing the strongest suppression effects. However, the design of this experiment did not permit the conclusion that repetition suppression scales with firing rate irrespective of stimulus novelty. In our experiment, the confound between stimulus novelty and stimulus efficacy was eliminated. Our results confirm that repetition suppression increases proportionally with the magnitude of the evoked visual response.

A second critical assumption required by the MR adaptation method is that repetition suppression is cell-specific, rather than stimulus-specific (Henson 2003). The logic of this claim is illustrated in figure 34. If one were to observe that the level of BOLD signal adaptation in LO is greater when prime and probe stimuli are identical, as opposed to when the probe image is a transformed version of the prime image (such as rotation, panel A), then the interpretation is that neurons in LO are viewpoint selective (panel B). However, viewpoint invariant neurons could also give rise to the same observation at the level of functional imaging, provided that neuronal suppression is mediated at the level of synaptic inputs rather than at the level of spiking output (panel C). In our study, we were primarily concerned with stimulus specific suppression, but we also observed non-specific effects at the beginning of each session (Figure 23). The extent to which both factors contribute to MR adaptation effects is likely to be highly sensitive to the duration of conditioning stimulus and the time interval between prime and probe. Accordingly, a

better understanding of the biological mechanisms that contribute to firing rate reductions in LO is clearly desirable.

Figure 34 (overleaf). Schematic of the pattern of BOLD response that would arise from a cell-specific vs. a synapse-specific mechanism of repetition suppression. **(A)** A viewpoint-tuned neuron, which responds strongly to a profile face view, but poorly to a frontal face view, or a non-face image. **(B-C)** The expected pattern of BOLD response is the same for view-tuned neurons regardless of whether repetition suppression is cell-specific or synapse-specific. Only repeated profile faces will induce MR adaptation because no other stimulus will evoke a strong initial response. **(D)** A viewpoint-invariant neuron, which responds strongly to both profile and frontal face views. **(E)** If repetition suppression is cell specific, then either face view will serve as an effective adapting stimulus. Therefore MR adaptation will be invariant to the image change. **(F)** Alternatively, if repetition is synapse-specific, MR adaptation will appear to be viewpoint tuned even though the neuron is not. Note that viewpoint-tuned vs. viewpoint invariant neurons only give rise to different patterns of BOLD response if repetition suppression is cell-specific (panels B vs. E).


A
Viewpoint-Tuned Neuron
Neural Response
B
Cell-specific adaptation
1st
2nd
C
Synapse-specific adaptation
1st
2nd
fMRI Response
D
Viewpoint-Invariant Neuron
Neural Response
E
Cell-specific adaptation
1st
2nd
F
Synapse-specific adaptation
1st
2nd
fMRI Response

4. General Discussion

4.1. Overview

The purpose of the experiments described in this thesis was to investigate the neural mechanisms that contribute to object representation. The experiment presented in chapter 2 investigated the rules governing visual feature integration at the level of individual neurons in IT. We demonstrated that selectivity for orthogonal features of objects are combined in a linear manner. The experiment presented in chapter 3 investigated the nature of visual response plasticity in IT that accompanies behavioral priming. The significance of our findings was discussed at a more technical level at the end of both chapters. Here, we review the relevance of our findings to the field of neuroscience at a more general level. The results from chapters 2 and 3 are considered separately. We begin each of the following sections by summarizing the main contributions that each project has made to our understanding of the neural mechanisms of object recognition. We conclude by identifying major questions that remain unresolved, and by identifying directions for future research.

4.2. Linearly independent selectivity for shape and color

The aim of the experiment presented in chapter 2 was to investigate the rules according to which IT neurons integrate information about stimulus identity from different feature dimensions. Previously, it had been well established that individual neurons in IT are selective for multiple feature dimensions simultaneously (Desimone 1984, Tanaka et al 1991, Komatsu and Ideura

1993). The fact that many neurons in anterior IT are selective for stimuli with highly complex and specific shape properties (Gross et al 1972, Tanaka et al 1991) has encouraged the interpretation that IT neurons respond specifically to objects that contain conjunctions of the neuron's preferred features (Tanaka et al 1991, Riesenhuber and Poggio 1999). A minority of neurons can be demonstrated to encode object shape irrespective of the local cues that define the object's edges (Sary et al 1993). This finding could be construed to imply that shape processing in IT is of special significance compared to non-shape feature dimensions (Biederman and Ju 1988, Aginsky and Tarr 2000). However, an alternative possibility is that some neurons in IT display cue-invariant shape selectivity, and other neurons display shape-invariant cue selectivity (Komatsu and Ideura 1993). In order to determine how information from multiple stimulus dimensions is integrated in IT, we recorded physiological responses to a set of stimuli in which the shape and color features were varied independently.

At the level of individual neurons in IT, we demonstrated that the majority of units integrate shape and color information in a linearly independent manner. At the level of the neuronal population, we demonstrated that selectivity for both shape and color features is distributed independently. A relatively small proportion of neurons displayed nonlinear sensitivity to shape-color conjunctions. For neurons in which significant evidence of conjunction coding was observed, the strength of such nonlinear effects was comparatively weak. Thus, a linear integration model accounts for a higher proportion of the variance in neuronal responses in IT that has been previously appreciated.

Our results suggest that linear coding might be a general principle of stimulus energy integration

that acts at multiple stages in the ventral visual pathway. This finding is of interest towards the development of a conceptual framework for discovering feature selectivity in IT neurons. The potential value of such a framework can be appreciated by considering the practical consequences, from the experimenter's perspective, of linearity in V1 neurons. Because spatial summation of luminance contrast in V1 receptive fields is linear, it is possible to infer the shape of the receptive field by combining evidence derived from different stimuli through simple addition. The practical advantages that derive from a linear systems approach has made it possible to ask questions about early visual cortex at an increasing level of sophistication. In particular, the method of reverse white noise correlation has been employed to characterize the integration of luminance contrast in V1 simple cells with considerable success (Reid et al 1987). More recently, the reverse correlation technique has successfully been extended to characterize selectivity for chromatic contrast in V1 simple cells (Horwitz and Albright 2005), for luminance contrast in complex cells (Touryan et al 2005), and for motion stimuli in area MT (Krekelberg et al, *Society for Neuroscience Abstracts* 2005). Applying the framework of linear systems analysis still farther beyond the striate cortex will shed light on the dimensions of the feature space that underlies high-level object representations.

4.3. Neural activity accompanying repetition priming

The aim of the experiment presented in chapter 3 was to investigate the relation between repetition priming at the behavioral level and repetition suppression at the level of single

neurons. Previously a causal relation between the two phenomena had been inferred, but had not been demonstrated (Desimone 1996, Wiggs and Martin 1998). The hypothesis that repetition priming is mediated by reduced activity in IT neurons was derived from four sources of evidence: First, stimulus repetition results in perceptual priming in humans (Tulving and Schacter 1990). Second, stimulus repetition results in reduced activation in the human brain region LO (Grill-Spector et al 1999). Third, BOLD signal reductions in LO are observed in human subjects engaged in behavioral priming tasks (Buckner et al 1998). Fourth, stimulus repetition induces firing rate suppression in single neurons in the monkey brain region IT (Li et al 1993). Thus, the argument that behavioral priming is mediated by neuronal suppression assumes a correspondence among experimental data derived from different experimental paradigms. The work described in chapter 3 constitutes a necessary step towards bridging the logical gaps that must be crossed in order to compare data obtained from human vs. monkey subjects, on the one hand, and from physiological vs. functional imaging methodologies, on the other hand.

Repetition priming has never been demonstrated before in monkeys. Accordingly, in order to assess the relation between priming and neuronal suppression, it was first necessary to develop a monkey model of priming. We accomplished this objective by training monkeys to perform the symmetry decision task. Using this behavioral paradigm, we demonstrated that IT neurons undergo repetition suppression under conditions that also induce behavioral priming. We did not detect a trial-by-trial correlation between measures of priming and suppression, which we would expect to find if the causality hypothesis were correct. However, this negative result might simply reflect the limits of sensitivity that could be overcome by refining our methods, rather

than a true absence of correlation between priming and suppression. More importantly, we demonstrated that repetition suppression results in scaling of neural responses in IT, rather than sharpening of neural selectivity. Our results shed light on two currently unresolved questions in the field of neuroscience. The first question is: what is the neural mechanism underlying perceptual priming in behavioral studies? The second question is: what is the mechanism underlying BOLD signal adaptation in functional imaging studies? We consider the implications of our findings to each of these questions in turn.

What is the neural mechanism underlying perceptual priming in behavioral studies?

In our physiological results, we demonstrated that repetition suppression does not result in narrower selectivity tuning curves in IT neurons. Accordingly, if repetition suppression does mediate behavioral priming, it must do so by some mechanism other than sharpening (Desimone 1996). Alternative models are suggested by the results of theoretical studies of object representations in neural networks.

Although the notion that narrower tuning curves should result in improved sensory processing is intuitively appealing, computational modeling studies indicate that this is not always the case. The relative advantages of sharpened vs. broadened tuning curves is a topic of active debate and research in theoretical neuroscience. In network models of spiking neurons with a high degree of correlated noise across units, narrower tuning curves perform poorly relative to broader tuning curves (Series et al 2004). More generally, Zhang and Sejnowski (1999) have argued that broader tuning curves result in better discriminative performance in units that are selective to multiple feature dimensions simultaneously, which IT neurons certainly are (Desimone et al

1984, Tanaka et al 1991, Komatsu and Ideura 1993). These theoretical findings suggest that sharpening might not have the beneficial effect on neural processing that intuition would suggest. Determining whether behavioral recognition would be more improved by sharper or broader tuning curves will require a better sense of whether the assumptions underlying these theoretical studies are biologically plausible.

Other computational modeling studies of object recognition and memory have revealed that a fundamental trade-off exists between the processing demands of pattern completion vs. pattern separation (Treves and Rolls 1992, O'Reilly and McClelland 1994). Considering how this trade-off is reflected in the coding scheme employed by brain areas mediating object recognition as opposed to memory formation suggests that perception might not be improved by selectivity sharpening in IT. Pattern completion is a critical process necessary for successful object recognition in the face of degraded visual input. Neural networks with broadly tuned units are optimal for pattern completion. In contrast, pattern separation is required for efficient storage of sensory representations in neural network models of memory. Sparse coding is required to achieve effective pattern separation. It has been suggested that the trade-off between the optimal constraints of object recognition and memory storage is the basis of the division of labor between the temporal lobe visual areas and the hippocampal formation (Treves and Rolls 1992, O'Reilly and McClelland 1994). Area CA3 of the hippocampus implements an extremely sparse coding scheme (Jung and McNaughton 1993), and possesses input pathways with synapses appropriate for mediating both pattern storage and retrieval (McMahon and Barrionuevo 2000). In contrast, IT employs a comparatively diffuse coding scheme (Young and Yamane 1992, Tovee et al 1995). Insofar as IT instantiates an object recognition network with broadly tuned units that are

optimized for pattern completion, selectivity sharpening would not be beneficial to perception.

An alternative theoretical account of repetition priming has recently been proposed, which makes reference to the fact that action potentials in a population of spiking neurons are more likely to synchronize if the range of firing rates among units in the network is narrow (Gotts 2003). The fact that repetition suppression follows a scaling rule indicates that repetition suppression will serve to reduce the variance in the distribution of firing rates across the population of responsive IT neurons, which in turn facilitates synchronous spiking. Within a broad range of biologically plausible parameters, the overall decrease in neural activity that results from repetition suppression is more than compensated for by the greater probability of spike transmission between pre- and postsynaptic neurons (Gotts 2003). A similar mechanism has been demonstrated to mediate experience-dependent enhancement of sensory processing in invertebrates. In the insect olfactory system, repeated exposures to odorant stimuli induces both decreases in firing rate and increases in synchrony in neurons in the antenna lobe (Stopfer and Laurent 1999). This result establishes that a functional relation exists between repetition suppression and synchrony that can result in a facilitation of sensory processing. In monkeys, synchrony has been implicated in contributing to attentional modulation of sensory processing. Spatial attention increases the spike-field coherence between action potentials in V4 neurons and the gamma band of the extra-cellular local field potential (Fries et al 2000, Bichot et al 2005). In light of our finding that repetition suppression results in scaling of neural responses in IT, it would be of interest to test whether repetition-induced scaling of visual responses is accompanied by increases in synchrony.

What is the mechanism underlying BOLD signal adaptation in functional imaging studies?

Our finding that repetition suppression results in linear scaling of evoked firing rate in IT constrains the interpretation of BOLD signal reductions induced by stimulus repetitions. Whereas the sharpening model is incompatible with the proposal that adaptation of weak BOLD responses is the result of a small number of neurons with high firing rates (Avidan et al 2002), the scaling model is compatible. Thus, at the level of the spike-output of IT neurons, our results the overall feasibility of the MR adaptation approach. Unresolved questions remain as to the biophysical mechanisms that mediate repetition suppression. As we argued in chapter 3, the interpretation of MR adaptation experiments depends critically on whether repetition suppression is mediated by cell-specific or synapse-specific mechanisms. Tuning properties of single neurons can only be inferred from stimulus specific adaptation of the BOLD signal if repetition suppression is cell-specific (Figure 34). Insofar as repetition suppression is synapse specific, neurons which are invariant to a given stimulus transformation might nonetheless fail to display an adaptation effect. This would be the case if a single neuron received input from separate afferent fibers that convey input signals arising from the original and transformed versions of the stimulus. In all likelihood, repetition suppression is mediated by a combination of factors at both the input and the output stages of neural integration and spiking. In our experiment, we observed some evidence for cell-specific suppression effects, in that visual responses decrease sharply over the initial twelve trials of each experimental session (Figures 16). The relative contributions of spike-frequency adaptation and short-term synaptic depression could be highly sensitive to the parameters of stimulation, such as the stimulus duration and inter-stimulus interval. Accordingly, a more complete understanding of the sub-cellular mechanisms underlying repetition suppression is clearly desirable. Future experiments in awake monkeys

will be necessary to characterize the temporal parameters of both stimulus-related and spiking-driven suppression effects. *In vitro* recording studies will be necessary to establish the relative contributions of both short-term synaptic plasticity and intrinsic membrane properties to repetition suppression in IT neurons. Such data will be invaluable to interpreting functional imaging studies of the human brain.

4.4. Summary and conclusions

In conclusion, the work described in this thesis has resulted in two contributions to our understanding of the neural mechanisms of object recognition. The first discovery is that stimulus selectivity in inferotemporal cortex is well characterized by a linear model of feature integration. This finding challenges the widely held assumption that high-level object representations are mediated by coding of feature conjunctions, and serves as a useful starting point for future investigations of linear mechanisms in high-level vision. The second discovery is that neurons in inferotemporal cortex exhibit repetition suppression under the same conditions that induce behavioral priming. This finding constitutes the first demonstration of repetition priming in monkeys, and establishes a new experimental paradigm for future investigations into the neural basis of implicit memory and learning in the visual system.

APPENDIX

General Methods

Surgical procedures.

Three rhesus macaque monkeys were used as experimental subjects (Chapter 2: Monkeys CA and EG; Chapter 3: Monkeys EG and PH). All experimental procedures were approved by the Carnegie Mellon University Animal Care and Use Committee and were in compliance with the guidelines set forth in the United States Public Health Service Guide for the Care and Use of Laboratory Animals. At the outset of the training period, each monkey underwent sterile surgery under general anesthesia maintained with isofluorane inhalation. The top of the skull was exposed, bone screws were inserted around the perimeter of the exposed area, a continuous cap of rapidly hardening acrylic was laid down so as to cover the skull and embed the heads of the screws, a head-restraint bar was embedded in the cap, and scleral search coils were implanted on the eyes, with the leads directed subcutaneously to plugs on the acrylic cap. Following initial training, a 2 cm diameter disk of acrylic and skull overlying the right hemisphere was removed to allow for the positioning of a vertically oriented cylindrical recording chamber. The chamber was centered at approximately anterior 18 mm and lateral 18 mm with

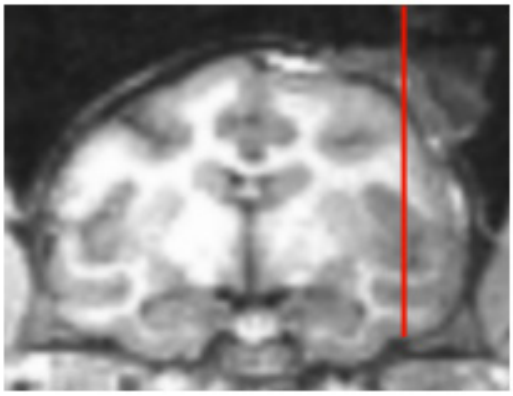


Figure. A-1. Coronal MRI section from monkey EG (Anterior 18 mm, Horsley-Clarke coordinates) one indicating the center of the recording chamber. The red line indicates the path followed to approach IT.

respect to the Horsely-Clarke reference frame (Figure. A-1).

Monitoring single-neuron activity and eye position.

At the beginning of each day's session, a varnish-coated tungsten microelectrode with an initial impedance of several megohms at 1 KHz (Frederick Haer & Co., Bowdoinham, ME) was advanced through the dura into the underlying cortex. The electrode was introduced through a transdural guide tube advanced to a depth such that its tip was approximately 10 mm above IT. The electrode could be advanced reproducibly along tracks forming a square grid with 1 mm spacing. The action potentials of a single neuron were isolated from the multi-neuronal trace by means of an on-line spike-sorting system using a template matching algorithm (Signal Processing Systems, Prospect, Australia). The spike-sorting system, on detection of an action potential, generated a pulse the time of which was stored with 1 ms resolution. Eye position was monitored by means of a scleral search coil system (Riverbend Instruments, Birmingham, AL) and the x and y coordinates of eye position were stored with 4 ms resolution. To measure saccadic reaction times, we first identified the saccade by locating the peak of the eye velocity trace. We then located the onset of the saccade, which was defined as the time prior to the velocity peak at which the eye velocity crossed a threshold of 15°/sec.

Estimation of visual latency.

To determine the mean latency of visual responses at the population level, we employed a procedure similar to the method used to determine saccade latency. This procedure is illustrated for the population firing rate histograms shown in Figure A-2 A. The first step was to compute the derivative of the population spike density function. We then located the peak of the derivative, which corresponded to the inflection point of the rising phase of the visual response.

We defined the onset of the visual response as the point at which the derivative exceeded 25% of the peak value. In order to test the hypothesis that the latency of visual response differed between first and second presentations, we performed a bootstrap analysis in which trials from the first and second responses were re-sampled to generate 1,000 new sets of simulated responses. The distribution of latency differences obtained from the simulated data sets was then used to set the significance thresholds for testing the hypothesis that the latencies from the first-presentation and second-presentation data sets were significantly different.

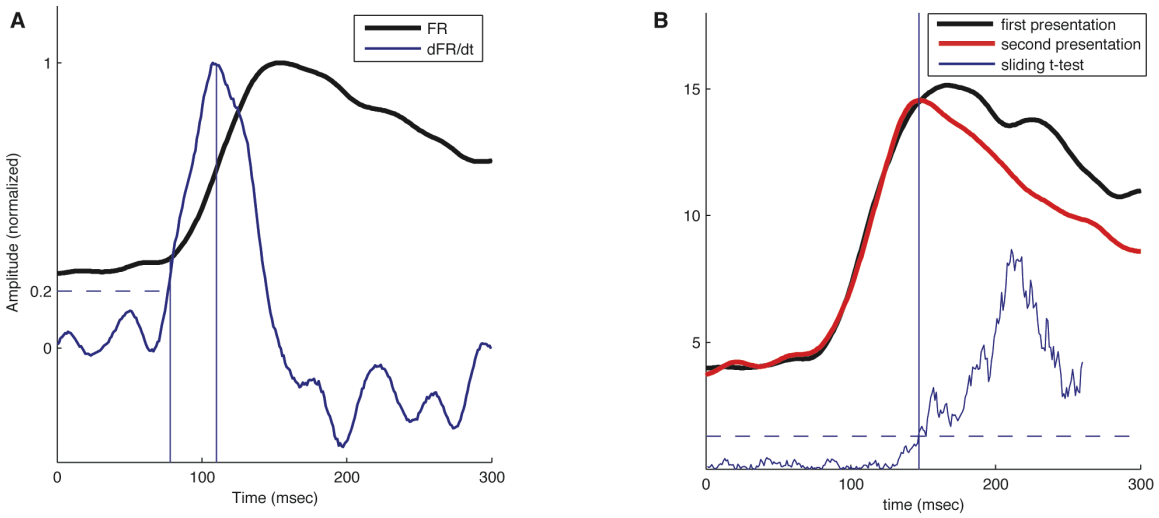


Figure A-2. (A) Method for determining the latency of visual responses, illustrated for population responses of lag 0 repeats. Normalized firing rate histogram (FR, black line) is plotted together with the temporal derivative of firing rate (dFR/dt, blue line). The derivative was used to determine the onset of the visual response. Visual response latency was defined as the time at which the derivative exceeded 20% of its peak value (80 msec). **(B)** Method for determining the latency of the repetition suppression effect, shown for population responses of lag 0 repeats. The black and red lines represent the visual responses on first and second presentations, respectively, at lag 0. The blue line indicates the significance level of a paired t-test comparing spikes from first vs. second presentation that occur within a 40 msec sliding boxcar window. Suppression latency was defined as the earliest point at which the responses to the first vs. second stimulus were significantly different at an alpha level of 0.05 (indicated by the dashed blue line) and remained so for 10 consecutive positions of the boxcar. The vertical blue line indicates the latency of neural suppression (150 msec) that was computed using this method.

To determine the latency of the suppression effect at the population level, we employed a method illustrated in Figure **A-2** B. Data were analyzed from all pairs of trials in which a neuron fired at least one spike during the interval from 80 to 280 ms following stimulus onset. Spikes were counted within a 40 ms sliding boxcar window that was moved incrementally in 1 ms steps. At each step, we used a two-sided, paired t-test to compare the firing rates evoked on the first and second presentations of each stimulus. The boxcar continued to slide until the result of the t-test indicated a statistically significant difference ($p < 0.05$) between the first and second presentation for ten consecutive steps of the boxcar. Having thus found a period of sustained differences between the two responses, we then identified the latency of suppression as the earliest time-point inside the first window in the string of ten significant locations of the integration window.

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