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Neural Mechanisms of Perceptual Learning

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Neural Mechanisms of Perceptual Learning

by

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Abstract

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Perceptual learning is a pervasive and specific improvement in the performance of a perceptual task with training. This dissertation examines the role of the neurotransmitter acetylcholine(ACh) in perceptual learning in a series of behavioral and pharmacological studies in healthy human subjects. ACh plays a role in cognitive functions such as attention and in animal models it has been found to play a role in the facilitation of neural plasticity.

The work described here focused on the learning of a visual motion direction discrimination task. In the first study described, I provide a theoretical framework for the study of learning of this task. This part examined the "oblique effect", an advantage in performing this task when stimuli are presented in cardinal, rather than oblique directions. I present both experimental evidence and a population coding model that indicate the oblique effect in behavior may rely on the unequal representation of oblique and cardinal directions in visual areas in cortex. The model suggests that the oblique effect relies on an interplay of this representation with the decoding of the stimulus in higher cortical regions.

In the second part of this thesis, participants were administered the cholinesterase inhibitor donepezil while training on the motion direction discrimination task, performed in oblique directions. As previously described, this training abolishes the behavioral oblique effect. Moreover, donepezil increased the effects of training on performance and the specificity of these effects to the oblique direction and the visual field location in which learning took place, suggesting that ACh directs learning towards cells encoding behaviorally relevant features of the stimulus.

The third part presents a study investigating the role of ACh in the allocation of voluntary visual spatial attention (which can be allocated in a goal-oriented manner) and involuntary attention (which is automatically captured by salient events). We used an anti-predictive spatial cueing task to assess the effects of pharmacological enhancement of cholinergic transmission on behavioral measures of voluntary and involuntary attention. We found that cholinergic enhancement with donepezil augments the benefits of voluntary attention but

does not affect involuntary attention, suggesting that they rely on different neurochemical mechanisms.

Taken together, the results of the second and third parts of this thesis provide converging evidence for a potential mechanism of learning: ACh mediates the allocation of voluntary attention, which in turn provides a necessary substrate for learning to occur.

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I would like to start by thanking my advisor, Michael Silver. I am grateful to him for sharing his clear and incisive thinking about scientific problems and also his optimism in doing science. I am thankful for the nurturing environment he has created in his lab, for encouraging me to tackle challenging projects and for his faith in me and my work. I am very grateful for the freedom he has given me to explore and learn new things while I was working on this dissertation and for all the opportunities he has given me to do interesting science.

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Dedicated to my grandfathers

Abraham Hasan and Harry Rock

Contents

Chapter 1

Introduction

1.1 Perceptual learning

Learning from experience underlies our ability to adapt to novel situations and new environments. The human nervous system has evolved to contain a set of powerful mechanisms to facilitate the process of learning and understanding these mechanisms is one of the central goals of neuroscience. This goal is being pursued at a variety of different levels, ranging from the study of molecular mechanisms of synaptic plasticity [Pittenger and Kandel, 2003] to the study of learning of complicated rule-based behaviors in humans [Bunge, 2004]. The work presented in this dissertation focuses on the role of a particular molecule, the neurotransmitter acetylcholine, in facilitating changes that may occur in the visual system of human subjects as they learn and improve in the performance of a simple visual discrimination task.

Classical findings in neurophysiology have suggested that experience-dependent changes occurring in the visual system during development are limited to a period early in life. Once this so-called 'sensitive period' is over, substantial changes in neural representation are less likely to occur [Hubel and Wiesel, 1970]. In humans, the sensitive period for this kind of plasticity in the visual system is thought to extend until approximately age 4 [Banks *et al.*, 1975]. However, humans can develop sensory expertise well beyond the age of 4. This phenomenon occurs naturally, when people develop expertise in some field of knowledge requiring subtle sensory discriminations, such as bird-watching or mushroom-hunting.

In the laboratory, this phenomenon can be studied under controlled conditions by training subjects on the performance of a particular perceptual task. The pervasive, stimulus-specific improvement in the performance of a task is referred to as perceptual learning [Fahle and Poggio, 2002]. The study of perceptual learning has demonstrated that humans are able to substantially improve in the performance of perceptual discriminations, even in adulthood.

In addition to serving as a model for studying physiological substrates of learning, perceptual training has been used to treat medical conditions such as dyslexia [Temple *et al.*, 2003] and amblyopia [Levi and Polat, 1996; Polat *et al.*, 2004; Levi and Li, 2009]. Thus,

understanding the neural mechanisms underlying perceptual learning has consequences for basic science as well as clinical implications.

The specificity of perceptual learning has been demonstrated for spatial location [Dill, 2002], color and spatial frequency [Fiorentini, 2002], ocularity, when training is monocular [Fahle *et al.*, 1995; Karni and Sagi, 1991], and orientation of stimulus elements in the display [Ahissar and Hochstein, 2002] and direction of their motion [Ball and Sekuler, 1982]. This specificity is often interpreted as indicating changes in stimulus coding by neural populations that are selectively tuned for the dimension in which specificity is found. For example, if perceptual learning does not generalize across different visual field locations (that is, learning to perform a perceptual discrimination in one visual field location does not improve performance of the same task in other visual field locations), this indicates that changes have occurred in a population of cells that have spatially-specific receptive fields.

Studies conducted in humans, using fMRI, have documented substantial changes associated with learning occurring in areas as early as primary visual cortex [Furmanski *et al.*, 2004; Schwartz *et al.*, 2002; Yotsumoto *et al.*, 2008]. On the other hand, studies using single-cell recordings in non-human primates suggest that changes in early stages of visual processing may be rather limited [Schoups *et al.*, 2001; Ghose *et al.*, 2002], but that changes in subsequent areas may be more substantial [Yang and Maunsell, 2004; Law and Gold, 2008].

Importantly, a variety of factors, such as task difficulty [Ahissar and Hochstein, 1997] and the sequence of stimuli presented [Zhang *et al.*, 2008] affects the pervasiveness and specificity of learning, complicating the interpretation of the physiological results. In addition, recent physiological [Law and Gold, 2008], psychophysical [Xiao *et al.*, 2008; Zhang *et al.*, 2009], brain imaging [Mukai *et al.*, 2007], and computational [Law and Gold, 2009] studies on perceptual learning implicate higher-level cortical areas related to perceptual decision-making processes. To summarize, the neuronal substrates of perceptual learning and the rules governing changes occurring in the nervous system with perceptual learning are still not understood.

1.2 The oblique effect: learning the statistics of the natural environment?

The statistics of our natural environment are not uniform or isotropic. The distribution of spatial frequencies is skewed towards lower spatial frequencies [van der Schaaf A. and van Hateren, 1996] and the stimulus orientation [van der Schaaf A. and van Hateren, 1996] and motion direction distributions [Dakin *et al.*, 2005] contain an over representation of the cardinal orientations/directions(up/down, right/left).

In order to efficiently code information about the visual environment, the structure of the visual system should reflect the statistics of the natural environment [Simoncelli and Olshausen, 2001], including these anisotropies. For example, the non-uniform distribution of

orientations is reflected in the statistics of orientation preferences in primary visual cortex [Li *et al.*, 2003; Furmanski and Engel, 2000]. Additionally, thresholds in the performance of perceptual tasks on stimuli with orientation or motion direction that is parallel to the cardinal axes are often found to be lower than for stimuli parallel to the oblique (off-cardinal diagonals). This phenomenon is often referred to as the oblique effect [Appelle, 1972].

However, it is unclear whether these anisotropies in behavior and neural representation are a consequence of a genetically predetermined program, as suggested by the finding that members of different ethnic groups differ in the magnitude of the oblique effect [Timney and Muir, 1976; Ross and Woodhouse, 1979] or whether they are a consequence of exposure to these statistics in early development and/or later in life.

One approach to studying this question is taken by providing human subjects with controlled exposure to a stimulus which differs from the statistics of the natural environment and examining the consequence of this exposure. Indeed, perceptual learning of oblique directions of motion or orientations has been found to abolish the oblique effect in motion direction discrimination [Ball and Sekuler, 1982], as well as detection of low-contrast oriented gratings [Furmanski *et al.*, 2004]. In addition to showing that the behavioral oblique effect can be abolished through training, Furmanski et al. [Furmanski *et al.*, 2004] also showed that this change in performance corresponds to a reduction in the oblique effect in the neural representation of different orientations in primary visual cortex. Taken together, these findings suggest that at least some of the anisotropies in neural representation may be altered through experience.

1.3 The problem of learning

Because of the change that it requires, learning poses a challenge to representation by the nervous system. On the one hand, in order for learning to occur, some change must occur in the manner in which stimuli are represented in the nervous system. On the other hand, if the system constantly changes, how can stable representations be maintained and consistently retrieved?

Theoretical models of associative memory functions (e.g. [Hopfield, 1982]) suggest that retrieval of stored memories relies on intrinsic excitatory connections in cortex. However, these models usually focus on the dynamics of the network during memory retrieval, assuming that a pattern of connections has already been established. If learning is allowed to continue during retrieval, this might result in interference between memory retrieval and memory storage [Hasselmo, 1993].

This problem implies that the nervous system must somehow balance flexibility and stability in a way which allows changes to occur in some situations and not in others. One potential solution to this problem is to provide a signal which modulates the contribution of the intrinsic excitatory signals required for retrieval relative to the activity of neurons coding

the incoming signal from the sensory organs. One candidate to serve as such a signal is the neurotransmitter acetylcholine (ACh) [Hasselmo, 1993; Sarter *et al.*, 2005].

Cholinergic neurons in the basal forebrain project widely to many parts of cortex, including primary sensory areas. The role of the cholinergic system in attention and learning has been studied extensively in animal models [Sarter *et al.*, 2003]. In particular, direct stimulation of the cholinergic system can induce stimulus-specific neural plasticity, even when no task is performed. This has been achieved in animal models by direct infusion of ACh into primary visual cortex [Greuel *et al.*, 1988] and by electrical stimulation of the nucleus basalis [Kilgard and Merzenich, 1998]. Temporal pairing of these manipulations with presentation of a specific stimulus induced changes in receptive fields of neurons in primary sensory cortex. These changes occurred even though the animal was not performing any stimulus-related task, suggesting that appropriate enhancement of the cholinergic system can effectively replace the effects of attention during perceptual learning(see 1.4).

Recent surveys of the literature [Giocomo and Hasselmo, 2007; Hasselmo, 2006] suggest that the mechanism by which ACh affects learning and attention is a shift in the balance of activity in cortical neurons from a dominant influence of lateral intracortical connections to a dominant influence of afferent excitatory projections, in line with the model presented in [Hasselmo, 1993]. This shift is thought to enhance encoding of the stimulus presented at the time ACh is released. This idea receives support from a recent study showing that the shift away from intrinsic cortical inputs towards afferent inputs can account for long-term changes in receptive fields that occur following basal forebrain stimulation [Froemke *et al.*, 2007].

Thus, ACh could provide a solution to the problem described above, by acting as a top down signal that informs cortex when it needs to change and when it should stay the same.

1.4 The role of attention in learning

The way in which top-down modulation of the activity in primary sensory cortex affects perceptual learning is still not completely understood. On the one hand, allocation of attention seems to be necessary for perceptual learning to occur. In studies of the neural correlates of plasticity in the auditory [Recanzone *et al.*, 1993] and somatosensory [Recanzone *et al.*, 1992] systems, learning and associated neural plasticity were enhanced when the animals performed a relevant task during learning, compared to when the animal was either passively exposed to the stimulus or occupied with performance of another task. Behavioral studies in humans have shown that perceptual learning of a certain discrimination does not occur if attention is not allocated to this discrimination, even if the subject is repeatedly exposed to the stimulus [Ahissar and Hochstein, 1993]. However, other studies have suggested that learning may occur even when attention is drawn away from the learned stimulus. Thus, repeated presentation of a dynamic random-dot stimulus in the periphery resulted in specific

learning of motion discrimination of that stimulus, even if a central attention-demanding task was simultaneously performed and the coherent motion in the dots was imperceptible [Watanabe *et al.*, 2001].

As mentioned above(1.3), ACh is thought to play an important role in the modulation of attention. ACh levels in cortex increase when an animal is engaged in a task requiring sustained attention [Arnold *et al.*, 2002] and performance in such tasks is impaired when the basal forebrain is lesioned [Muir *et al.*, 1994]. Pharmacological studies in humans (reviewed in Chapter 4) also suggest a role for ACh in attention.

Taken together, these results suggest that ACh may mediate the allocation of attention and that this allocation of attention then serves to induce the change required in order for learning to occur.

1.5 Outline of the dissertation

The main hypothesis of this work is that increasing the levels of ACh in the brains of healthy human subjects should increase perceptual learning. Previous studies have shown stimulus-specific changes to neural representation following experimentally-induced activity in the cholinergic system [Kilgard and Merzenich, 1998; Greuel *et al.*, 1988]. If perceptual learning in the human visual system reflects specific changes to neural representation in the visual cortex, these may also be mediated by the activity of the cholinergic system, in a similar fashion. Therefore, they could be enhanced by the administration of a drug that enhances transmission in the cholinergic system. To the extent that learning would be more specific under cholinergic enhancement, this would provide further support to the idea that learning occurs through a change in the neural representation of the specific trained stimulus, although it does not rule out the involvement of higher-level mechanisms as well. The mechanism through which ACh may be mediating the increase in specific learning in the previous studies mentioned above is by directing activity to populations of neurons responding to the stimulus presented [Sarter *et al.*, 2005], inducing plasticity in these neurons. This same physiological mechanism, of increased response to the presented stimulus, may also be underlying the role of ACh in mediating the allocation of attention. Thus, the role of attention in learning is also addressed by the pharmacological manipulation of the cholinergic system in the study of perceptual learning, albeit indirectly.

The study presented in Chapter 2 provides a theoretical background to discuss the changes observed in perceptual learning of motion direction discrimination. In this study, the oblique effect was studied using a novel psychophysical procedure. In addition, we have performed model simulations, that suggest that the oblique effect in motion perception arises from a combination of differences in the representation of oblique and cardinal directions in the visual system (presumably in primary visual cortex and area MT) and a particular decoding scheme employed by additional areas in cortex in order to decode the information

represented in those areas [Rokem and Silver, 2009].

Chapter 3 directly addresses the hypothesis presented above. As previously shown, the oblique effect can be abolished by specific training on a motion-direction judgement in an oblique direction [Ball and Sekuler, 1982]. In our study, subjects trained on a motion direction discrimination task on stimuli moving in an oblique direction. We employed a double-blind, placebo-controlled, crossover design in which each subject participated in two courses of training. In one course of training, the subjects' cholinergic system was pharmacologically enhanced and in the other course of training, subjects were administered a placebo. This allowed us to directly measure the effect of the drug on learning.

In Chapter 4, we provide more direct evidence for the role of ACh in the modulation of attention. In this study, we examined the consequences of pharmacological enhancement of the cholinergic system on performance of and attention cueing task. In addition to its bearing on the main hypothesis presented above, this study was also designed to delineate the role of ACh in the modulation of two different kinds of attention, voluntary (endogenous) attention and involuntary (exogenous) attention.

Chapter 2

A model of encoding and decoding in V1 and MT accounts for motion perception anisotropies in the human visual system

2.1 Introduction

Performance in visual tasks is often asymmetric, depending on the location, orientation, and/or motion direction of visual stimuli. In some cases, these differences in performance may stem from asymmetries that exist in the natural environment and can provide insight into the developmental origins of perceptual and behavioral asymmetries [Dakin *et al.*, 2005]. In addition, these asymmetries may be used to illuminate the mechanisms of neural encoding and decoding underlying the performance of visual tasks. In this work, we have used anisotropies in motion perception to investigate encoding and decoding of motion stimuli by the human visual system.

Thresholds for perceptual tasks performed on moving stimuli or on oriented stimuli are often lower for stimuli with orientation or direction of motion that is parallel to the cardinal axes (up/down,right/left) than for stimuli oriented or moving along the oblique directions (the off-cardinal diagonals), a phenomenon referred to as the oblique effect [Appelle, 1972]. This behavioral anisotropy probably stems from a more robust representation of cardinal orientations in the visual system. Furmanski and colleagues ([Furmanski and Engel, 2000; Furmanski *et al.*, 2004] showed that the oblique effect in detection of low-contrast gratings (lower detection contrast threshold for cardinal than for oblique directions) was correlated with a difference in the magnitude of primary visual cortical fMRI responses to presentation of cardinal and oblique gratings. In addition, in a large sample of cat primary visual cortical neurons, randomly sampled in many different experiments, there were more cells preferring cardinal than cells preferring oblique orientations [Li *et al.*, 2003]. In motion perception, thresholds for discriminating two similar motions of direction are higher when the stimuli

are centered at oblique directions compared to cardinal directions [Ball and Sekuler, 1982; Gros *et al.*, 1998; Dakin *et al.*, 2005]. By analogy with the oblique effect for stimulus orientation, we assume that the oblique effect for motion perception is also based on an anisotropy in the representations of different motion directions in the visual system. A significant proportion of cells in primary visual cortex is not only orientation selective but also direction selective [Hubel and Wiesel, 1959; De Valois *et al.*, 1982; De Valois *et al.*, 2000; Peterson *et al.*, 2004]. The preferred direction and preferred orientation are always approximately orthogonal in macaque V1 cells, based on responses to moving bar stimuli [Albright, 1984]. 2D motion direction information may not always be available to the cell, due to the aperture problem [Horn, 1986]. However, when 2D motion direction information is available to V1 neurons, preferred direction is independent of stimulus orientation [Pack *et al.*, 2003]. Therefore, it is reasonable to assume that there are more cells in V1 that show a preference for cardinal motion directions than cells that prefer oblique directions. Moreover, the average orientation tuning width of primary visual cortical neurons tuned to cardinal orientations was smaller than the average tuning width of those tuned to oblique orientations [Li *et al.*, 2003]. Therefore, the average tuning width of motion selectivity is likely to be smaller for cells representing the cardinal directions compared to cells preferring oblique motions, though this has not yet been tested experimentally in primary visual cortex.

We used two tasks to characterize the oblique effect in motion perception. The first, a motion direction discrimination task, exhibited an oblique effect in direction discrimination threshold and was used to identify the cardinal direction associated with lowest discrimination threshold and the oblique direction associated with highest threshold in each of our subjects. We then measured the tuning width of motion adaptation for these two directions. Estimates of the tuning width were obtained by measuring the strength of adaptation (magnitude of the motion aftereffect, or MAE) following prolonged viewing of a field of coherently moving dots in one of the two directions. Previous work has shown that the magnitude of the MAE for random dot kinematogram (RDK) adapter stimuli was greater when the adapter stimulus included a moderate range of directions compared to a single direction of motion [Hiris and Blake, 1992]. Thus, the relationship between MAE strength and the range of directions in the adapter stimulus allows estimation of the width of direction tuning of motion perception.

In our experiments, the RDK adapting stimuli were generated by assigning a direction to each dot from a distribution of directions centered on either a cardinal or oblique direction. The variance of this distribution determines the directional variance of the stimulus. Our results show that like motion direction discrimination performance, the tuning width of motion adaptation also exhibited an oblique effect: direction tuning was sharper for cardinal adapter stimuli than for oblique stimuli.

We constructed a computational model of encoding and decoding of motion information by cells in areas V1 and MT that accounts for the observed oblique effects in motion direction discrimination and tuning width of motion adaptation. The model contains a set of V1 units

with feedforward connections to a set of MT units. The V1 units are anisotropic in their representation of motion: V1 cells representing cardinal directions are more numerous, and their directional tuning widths are narrower than the tuning widths of V1 cells representing oblique directions. The tuning properties of MT cells are then inherited through feedforward projections from V1 cells.

Information about stimulus motion direction is then decoded from the activity in the entire population of MT cells (as in [Pouget *et al.*, 2000]). The decoding method is based on a maximum likelihood procedure [Jazayeri and Movshon, 2006]. Our model quantitatively accounts for the observed psychophysical results, generating oblique effects for motion discrimination and for motion adaptation tuning width. It also agrees with previous findings that the oblique effect for motion discrimination is only present for stimuli with low directional variance [Dakin *et al.*, 2005].

Our modeling results demonstrate that oblique effects in motion perception could arise from a combination of an anisotropy in the encoding of the stimulus by the visual system and a decoding mechanism that employs a statistically optimal strategy to read out this information. This suggests that complex perceptual phenomena such as the oblique effect should be understood as a consequence of specific encoding and representation schemes as well as specific decoding strategies employed by the brain.

2.2 Methods

2.2.1 Subjects

Subjects were 16 young adults (6 female, mean age 24.1±3.3 years) with normal or corrected-to-normal vision. All subjects were naïve to the purpose of the experiment and had no prior experience in performing psychophysical tasks. All subjects provided written informed consent, and the experimental protocols were approved by the Committee for the Protection of Human Subjects at the University of California, Berkeley.

2.2.2 Stimuli and experimental procedures

Stimuli were produced using the Psychophysics Toolbox [Brainard, 1997; Pelli, 1997] for Matlab (Mathworks, Natick, MA) on Macintosh OS 10 (Apple, Cupertino, CA). The stimuli were presented on a Multisync FE992 CRT monitor (NEC, Tokyo, Japan) at a screen resolution of 600 by 800 and a refresh rate of 85 Hz. The edges of the screen were obscured with a circular cardboard aperture that eliminated any cues that could have been provided by the corners of the monitor frame. Similarly, a circular fixation point was used to eliminate the possibility of orientation cues. Subjects were seated comfortably and used a chin rest to insure consistent presentation of the stimuli.

2.2.2.1 Experiment 1: motion direction discrimination

Stimuli were random dot kinematograms(RDK). The RDKs were presented within a circular annulus covering 1.0 - 3.1 degrees radius from the fixation point. The RDKs always contained 100% coherent motion. However, dots moved to another position in the annulus after a lifetime of two monitor refresh frames in order to prevent the possibility of extracting the direction of the stimulus by tracking a single dot. Dots were approximately square and were 4.8 arcminutes in size. The dot density was approximately 2 $dots/degree^2$, and the dot velocity was 13 $degrees/second$.

In each trial (see Figure 2.1A for the trial structure), subjects viewed a 500 msec RDK stimulus followed by a 200 msec interstimulus interval and then another 500 msec RDK stimulus. The stimuli moved in the same direction in half of the trials and moved in different directions, separated by a small angle, α, in the other half. In the trials for which two different directions were shown, the first or the second stimulus (randomly selected for each trial) had a standard motion direction that was maintained throughout a testing block. For the remaining trials in which the stimuli had the same direction, the two stimuli could be the standard for that block, $standard + \alpha$, or $standard - \alpha$. Subjects were asked to respond whether the stimuli were moving in the same or in different directions within a 625 msec response period. They received auditory feedback following each trial.

A brief training session was administered prior to the first testing session to verify that the subjects understood the instructions and to acclimate the subjects to the task. Then, four testing sessions were administered. Each testing session was divided into 8 blocks of 50 trials each. In each block, the standard stimulus was kept constant and was one of the cardinal directions or one of the off-cardinal diagonals (oblique directions), randomly assigned to each block. The difference between the standard and comparison stimulus was adjusted in each trial according to the QUEST algorithm[Watson and Pelli, 1983], and the threshold in each block (for $\sim$ 80% correct performance) was estimated according to this algorithm. Thresholds were defined as the average of the four estimates for each of the eight directions. Subjects were given the opportunity to rest between blocks.

2.2.2.2 Experiment 2: MAE tuning width measurement

RDKs were presented in a circular region with a radius of 4 degrees around the fixation point. Each block of 50 trials began with presentation of an adapting stimulus for 40 secs (Figure 2.1C). Then, at the beginning of each trial, the adapting stimulus was presented for an additional 4 sec (top-up adaptation). Following a 50 msec interstimulus interval, a test stimulus was presented for 500 msec. Subjects were required to indicate whether the stimulus was moving in the same direction as the adapting stimulus or in the opposite direction [Blake and Hiris, 1993]. Responses were collected during a 625 msec response interval. The motion coherence of the test stimulus was adjusted in each trial according to the responses in previous trials, based on a 2-up/1-down staircase (converging on $\sim$ 70%

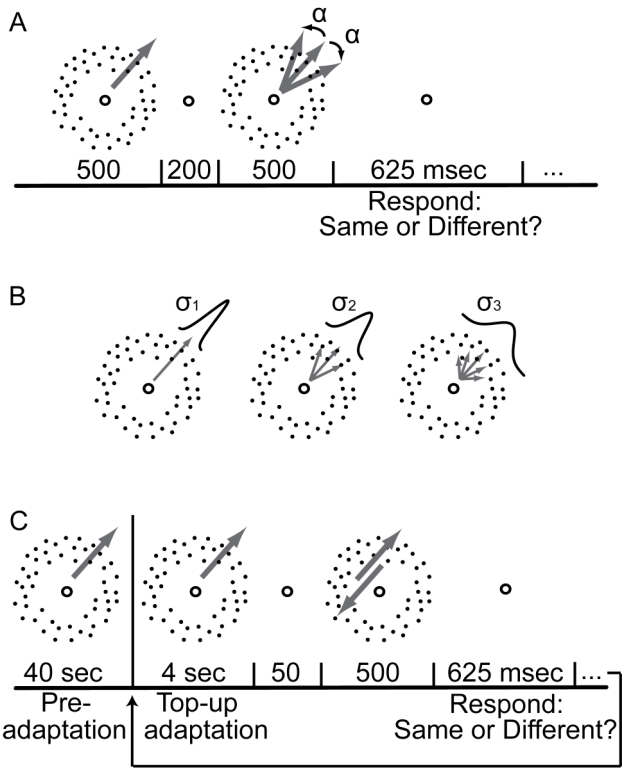

Figure 2.1: *Task design*. *A*: Motion direction discrimination task. Subjects observed motion in a standard direction, followed by either motion in the standard direction or motion in a direction similar but not identical to the standard direction. During the intertrial interval, subjects reported whether the two stimuli were moving in the same direction or not. *B*: Motion aftereffect task. Adapting RDK stimuli spanned a range of variances of motion directions. The directional variance was controlled by drawing the motion direction of each dot from Gaussian distributions with different widths (standard deviations). *C*: Motion aftereffect task. Subjects were initially presented with 40 seconds of an adapting stimulus. Then, at the beginning of each trial, there was an additional period of top-up adaptation. Subjects then made a direction judgment on a probe RDK with low motion coherence. The strength of adaptation was determined by measuring the amount of coherence that was needed in order to counteract the MAE

correct performance). The threshold was then determined by fitting a cumulative Weibull distribution to all the trials in the assessment. The goodness of fit was determined for each psychometric function, and thresholds that did not conform to a Weibull function [Evans *et al.*, 1989] were excluded from additional analysis. Specifically, we excluded all thresholds that did not have at least a a 99% probability of coming from a Weibull distribution [Watson, 1979].

A brief training session was administered for each subject to verify that he or she understood the instructions and was acclimated to the task. Then, each subject participated in four testing sessions. In two of the testing sessions, the adapting direction was the oblique direction for which the subject's threshold in Experiment 1 was highest. In the other two sessions, the adapting direction was the cardinal direction for which the subject's threshold in Experiment 1 was lowest. The order of administration of these different directions was counterbalanced across subjects. In each testing session, 8 blocks were administered. Blocks differed in the variance of directions of motion that were present in the adapting stimulus. Stimulus variance was manipulated by assigning a motion direction to each dot in the RDK from a Gaussian distribution (Figure 2.1B). The distribution mean was the adapting stimulus direction, and the standard deviation of the Gaussian determined the directional variance for that block of trials. The standard deviations used were 0 (no variance, all dots moved in the same direction), 2.8125, 5.625, 11.25, 16.875, 22.5, 45, and 90 degrees.

2.2.3 Computational model of motion processing in visual cortex

2.2.3.1 General model structure

The model consisted of one layer representing motion direction selective V1 cells and one representing MT cells. V1 units projected in a feedforward manner to the MT units, whose firing rate was determined from the activity of their inputs from V1 cells and the strength of the synaptic connections between each V1 cell and each MT cell. Finally, the direction of the stimulus was decoded from the activity across the population of MT cells using a maximum likelihood procedure.

Following the physiological evidence from primary visual cortical neurons [Li *et al.*, 2003], directional anisotropies were implemented in the V1 layer. Thus, there were more cells representing cardinal directions in the V1 layer, and the mean tuning width of these cells was narrower than the tuning width of cells representing oblique directions. The MT cells inherited these anisotropies through a homogenous set of connections between V1 and MT.

The different stimulus variance conditions were simulated by providing each V1 unit with an instance of one direction of motion for each iteration of the model. This simulated the RDK used in the experiments, under the assumption that each dot in the RDK excited one V1 unit. The directions of motion of the inputs to the V1 cells were drawn from a distribution of directions, and the variance of this distribution corresponded to the directional variance

of the stimulus. Before being passed to the MT units via the synaptic connections between the layers, the output of every V1 unit was normalized by the sum of the activity of the entire population of V1 cells. Then, activity in each MT unit was computed, based on the activity in the connected V1 cells. Finally, the stimulus direction was decoded from the activity of the population of MT units using a maximum likelihood procedure. We adopted the convergence level used by Rust et al. [Rust *et al.*, 2006] of 12 V1 cells for each MT cell. Our complete model contained 32 MT units and 384 V1 units.

2.2.3.2 Generating model activity

In the first layer, representing V1 cells, the firing rate of each unit as a function of stimulus direction was described by a circular Gaussian distribution, also known as a von Mises function [Patel and Read, 1996]. This is a bell-shaped tuning curve of the form:

$$f(\theta) = a_{V1} e^{\frac{cos(\theta - \theta_0)}{Z}} + b_{V1} \tag{2.1}$$

θ_0 is the unit's preferred direction, b_{V1} is the spontaneous rate of the unit (set to 10 Hz for all V1 units), a_{V1} is the maximal stimulus-evoked response to a stimulus moving in the preferred direction (set to 100 Hz for all V1 units), and $Z = 1/(\sigma \cdot 360 \cdot I_0(1/\sigma))$. Z determines the width of tuning. $I_o(x)$ is a zero order Bessel function of the first kind of x. The tuning width of each V1 cell was set according to the cell's preferred direction:

$$\sigma(\theta_0) = \gamma(1 - cos(4\theta_0)) + \epsilon \tag{2.2}$$

γ is a parameter that determines the ratio between the maximal tuning width (occurring in the cells tuned to oblique directions) and the minimal tuning width (occurring in cells tuned to cardinal directions). This minimal tuning width is represented by ϵ and was set to 45 degrees. In addition, V1 cells were distributed unevenly along the different directions, according to the following equation:

$$\rho(\theta_0) = \frac{\beta(1 - cos(4\theta_0)) + \delta}{360} \tag{2.3}$$

β is a parameter that determines the ratio between the densest representation (the difference in degrees between cells with preferred directions around the cardinal directions) and the sparsest representation (the difference between cells with preferred directions around oblique directions), and δ corresponds to the smallest difference between the preferred directions in the representation of cardinal directions, set to 1. In the results presented here, β and γ were set to 1.2 and 2, respectively. However, as verified by an extensive study of the parameter space, similar results were obtained over a range of values of β and γ. In each trial, the firing rate of each cell was determined by randomly choosing θ from a distribution with the mean set to be either a cardinal or an oblique direction (in different runs of the

model simulation) and with a standard deviation corresponding to the directional variance of the stimulus tested in that trial. This θ determined the mean response of the cell, based on its directional tuning curve. The activity of the cell in each trial was then determined according to a Poisson distribution:

$$P(r|\theta) = \frac{f(\theta)^r}{r!}e^{-f(\theta)} \tag{2.4}$$

In practice, r was determined for each V1 unit and each trial by drawing a number from a Poisson random number generator with mean equal to the firing rate of the cell in response to that trial's stimulus, or f(θ). Before passing the V1 outputs to the MT cells, a static nonlinearity (a squaring) was applied to the output of the V1 cells, and divisive normalization was applied to this squared output:

$$\hat{r}_i = \frac{r_i(\theta)^2}{\sum_{j \in V1} r_j(\theta) + \zeta} \tag{2.5}$$

where ζ is a parameter which controls the relative contribution of the other V1 units to reducing activity of a given V1 unit. An exploration of different values of ζ verified that the results are qualitatively the same as long as the output of this stage was between the noise level (b_{V1} in Equation 2.1) and the gain of the firing rate (a_{V1} in Equation 2.1). The connectivity for each pair of V1 and MT cells was defined according to a von Mises function:

$$w_{ij} = a_{MT}e^{\frac{cos(\theta_i - \theta_j)}{Z}} + b_{MT} \tag{2.6}$$

i is an index of the MT cell and j is an index of the V1 cell, $a_{MT} = a_{V1} = 100Hz$ and $b_{MT} = b_{V1} = 10Hz$. As in Equation 2.1, Z determines the direction tuning width of the connectivity between V1 and MT. Z was set such that the direction tuning width of the connectivity was always equal to 45 degrees, independent of the preferred direction of the units. The inputs to each cell were set such that the sum of the synaptic weights to the population of MT cells was the same for all possible stimulus directions. The firing rate of each MT cell, $f_i(\theta)$, was then determined by summing over all of its inputs from V1:

$$f_i(\theta) = \sum_{j \in V1} e_{ij}(\theta)\hat{r_j}(\theta) \tag{2.7}$$

The activity for each MT cell and each trial was then determined by drawing a number from a Poisson number generator, as in Equation 2.4. The resulting profile of activity in MT is the population code on which decoding then proceeds.

2.2.3.3 Decoding

Decoding of the direction of motion from the activity of the population of MT cells was done according to a statistically optimal scheme. Under this scheme, we are interested in finding the motion direction θ which is maximally likely, given a certain distribution of activity in the population of MT units, rMT. That is:

$$\hat{\theta} = argmax_{\theta} P(\theta|r_{MT}) \tag{2.8}$$

Here, $\hat{\theta}$ is the direction of motion that maximizes the likelihood of θ given a particular profile of MT activity r_{MT}. However, the functional form of this likelihood is unknown. Bayes's theorem states that the likelihood of θ given r_{MT} and the inverse likelihood, of r_{MT} given θ, or $P(r_{MT}|\theta)$, are closely related:

$$P(r_{MT}|\theta) = \frac{P(\theta|r_{MT})P(r_{MT})}{P(\theta)} \tag{2.9}$$

Therefore, assuming that the prior probability distributions for both θ and r_{MT} are flat (the probability of activity is the same for all units and no direction is more likely to appear than any other direction):

$$argmax_{\theta} P(\theta|r_{MT}) = argmax_{\theta} P(r_{MT}|\theta) \tag{2.10}$$

As described above (Section 2.2.3.2), the actual likelihood functions of activity in the MT cells, given θ, are independent Poisson processes. Therefore, the likelihood of the population activity of all the MT cells, given θ, a sum of these probabilities, is also a Poisson distribution [Pitman, 1993] which resembles the Poisson distribution that characterizes the firing rate of individual units (Equation 2.4):

$$P(r_{MT}|\theta) = \frac{f_{MT}(\theta)^{r_{MT}}}{r_{MT}!} e^{-f_{MT}(\theta)} \tag{2.11}$$

In practice, we approximate and maximize the following log likelihood function [Seung and Sompolinsky, 1993; Jazayeri and Movshon, 2006], which is derived by taking the log of equation 2.11:

$$LogL(\theta) = \sum_{i \in MT} logP(r_i|\theta) = \sum_{i \in MT} r_i log f_i(\theta) - \sum_{i \in MT} f_i(\theta) - \sum_{i \in MT} log(r_i!) \tag{2.12}$$

The last term can be dropped, as it does not depend on θ. The second term can also be dropped, as the model was constructed so that the total firing rate does not depend on the direction of the presented stimulus. Specifically, the sum of the inputs to the population of MT cells was set so that it was independent of stimulus direction. Therefore, Equation 2.12

reduces to:

$$LogL(\theta) = \sum_{i \in MT} r_i log f_i(\theta) \tag{2.13}$$

The tuning curves of cells in the MT layer, $f_i(\theta)$, result from both the tuning curves of the V1 cells as well as the connectivity between the V1 and MT layers. Therefore, we do not have an analytical form of these tuning curves. However, there is an empirical form of the tuning curve for each MT cell which can be derived by summing the V1 tuning curves and assigning a weight to each V1 tuning curve corresponding to the strength of the V1/MT synapse:

$$f_i^{emp}(\theta) = \sum_{j \in V1} w_{ij} f_j(\theta) \tag{2.14}$$

These empirically derived tuning curves resemble the form of the circular Gaussian V1 tuning curves described by the von Mises function (Equation 2.1). Therefore, we also approximated the tuning curve for each MT cell by a von Mises function:

$$f_i(\theta) \approx a_i e^{\frac{cos(\theta_i - \theta_j)}{Z}} + b_i \tag{2.15}$$

The parameter a_i, describing the tuning width of the unit was estimated from the width of the empirically derived tuning curve (Equation 2.14) at half maximum. Following [Jazayeri and Movshon, 2006], the approximate log-likelihood function is then the log of each unit's tuning curve, weighted by the inverse of its relative tuning width and by the activity of the unit in a given trial. This quantity was summed over the population of units in MT:

$$LogL(\theta) \approx \sum_{i \in MT} r_i \frac{\kappa_i}{\sum_{j \in MT} \kappa_j} cos(\theta - \theta_i) \tag{2.16}$$

where r_i is the activity of the cells for a given trial and θ_i is the inverse of the tuning widths as estimated from the empirical tuning curves (a_i in equation 2.15). In this sum, the cells with smaller tuning widths are weighted more heavily than the cells with larger tuning widths. For each iteration of the model, we used an unconstrained nonlinear optimization algorithm (implemented as the Matlab function `fminsearch`) to find a value of θ that maximizes this log-likelihood function, given the population response in MT.

2.2.3.4 Estimating the MAE strength

In order to simulate the MAE, we presented the model with a stimulus of 0% coherence following an adapting stimulus. The response amplitude of most MT cells decreases following adaptation to motion stimuli [Petersen *et al.*, 1985]. This reduction in amplitude may actually be greater when the adapting direction is slightly different from the preferred

direction [Kohn and Movshon, 2004]. However, for simplicity, we modeled adaptation in MT such that the adaptation in each unit was proportional to the response to the adapting stimulus. Thus, the strongest adaptation occurred in cells tuned to the adapting stimulus. The activity in response to the probe stimulus (with 0% coherence) was then calculated for the V1 cells and propagated to the cells in the MT layer (for simplicity, we assumed that V1 cells do not adapt). The firing rate in each MT cell in response to the probe stimulus was calculated based on a combination of its V1 inputs and the adaptation state of the MT cell. Thus, each cell's response to the adapting stimulus was multiplied by a factor that determines the strength of adaptation. The value of this factor can vary rather substantially without significantly affecting the results, as long as the firing rates do not become negative. For each cell, the firing rate during adaptation was subtracted from the firing rate that would have been obtained in the post-adaptation probe stimulation, had there been no adaptation. The actual firing is then derived from the Poisson distribution, as described above (Equations 2.4 and 2.11). The MAE strength was estimated from the ratio of the likelihood of the adapting stimulus and the stimulus moving in the opposite direction. This ratio can be calculated from the difference between the log likelihood functions of the two directions [Jazayeri and Movshon, 2006]. We compared the likelihood ratios to the value of the likelihood ratio when the adapting stimulus had a standard deviation of 0 degrees.

2.2.3.5 Estimating the direction discrimination threshold

In each presentation of a stimulus to the model, the θ that maximized the log likelihood function (Equation 2.13) was considered to be the direction perceived by the observer for that stimulus presentation. However, due to variability of the neuronal responses across presentations of the same stimulus, this maximum-likelihood direction varied between presentations of the same stimulus. The level of variability limited the fidelity of the representation of motion direction. This limit corresponds to the threshold obtained from the two alternative forced choice procedure employed in our psychophysical experiments (Figure 2.1A). We quantified this variability by estimating a distribution of the differences between the perceived stimuli in two consecutive presentations of the same stimulus. The model was iterated 100 times. For each iteration, the same stimulus was presented twice in succession, and the observed stimulus was decoded for each presentation (see Section 2.2.3.3). The difference between the two decoded stimuli was denoted $\Delta\theta$. Over the 100 iterations of the model, we constructed a distribution of $\Delta\theta$. We defined the median of the distribution of $\Delta\theta$ for a given condition (direction and standard deviation) to be the threshold for that condition [Han *et al.*, 2007; Kim and Bao, 2007], in order to satisfy the 50% guess rate in the two alternative forced choice paradigm used in the psychophysical measurements of direction discrimination thresholds.

2.2.3.6 Alternative decoding mechanisms

Two alternative decoding mechanisms were tested. Vector averaging involves computation of a weighted average over all of the cells in area MT. Each cell contributed a vector pointing in the direction best represented by its inputs and proportional in size to its firing rate. Then, the vectors were summed. The direction of this summed vector was considered to be the predicted stimulus direction. This mechanism has been proposed for other neural populations [Georgopoulos *et al.*, 1986] and for MT neurons, under some conditions ([Zohary *et al.*, 1996; Nichols and Newsome, 2002]. The strength of the MAE was estimated in a manner similar to the one described above (Section 2.2.3.4). A stimulus with 0% coherence was presented to a population of cells, following adaptation. Then, the MAE strength was considered to be the relative length of the projection of the population vector in the direction opposite to the adapting direction. The other alternative decoding mechanism we considered was a winner-take-all mechanism. Here, the decoding of MT activity occurs by identifying the cell with the most activity and assigning the predicted direction to the optimal direction for that cell, computed from the cell's inputs. This has also been suggested to be a decoding mechanism of activity in MT under certain circumstances [Salzman and Newsome, 1994; Zohary *et al.*, 1996]. Here, the MAE strength corresponded to the ratio of the activity in the cell preferring the adapting direction and the activity in the cell preferring the direction opposite to the adapting direction.

2.3 Results

2.3.1 The oblique effect in motion direction discrimination

To compare perceptual abilities for different directions of motion, we employed a motion direction discrimination task. Subjects viewed an annulus centered at the fixation point and containing a random dot kinematogram (RDK). For each trial, two RDKs were presented in succession. Subjects were required to press a button to indicate whether the RDKs were moving in the same or different directions (Figure 2.1A). For half of the trials, the RDKs were moving in the same direction in both intervals. For the other half of the trials, the motions were different, separated by a small angle α. The magnitude of α was adaptively adjusted based on a psychophysical staircase and according to the subject's previous performance. Discrimination thresholds were obtained for each subject for eight different directions. We found a robust and reliable oblique effect in the direction discrimination task: the mean threshold ($\sim 80\%$performance) for direction discrimination was 12.4 ± 9.0 degrees for cardinal directions and 17.9 ± 10.9 degrees for oblique directions (Figure 2.2). This difference was statistically significant (within-subject paired t-test, n=16, $p < 0.001$) and replicates previous findings of a robust oblique effect in similar tasks [Ball and Sekuler, 1982; Gros *et al.*, 1998].

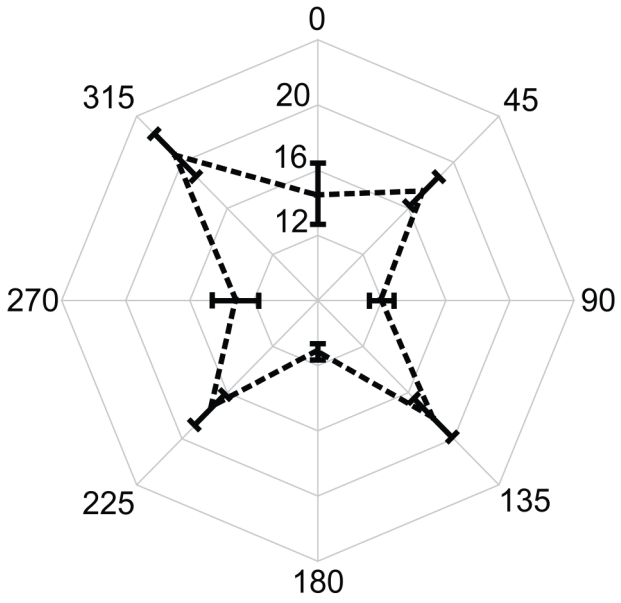

Figure 2.2: *The oblique effect in motion direction discrimination.* Average thresholds ($\pm 1 SEM$) from the direction discrimination task (Figure 2.1A) are presented. There was a robust oblique effect - mean thresholds for cardinal directions were always lower than mean thresholds for oblique directions. Numbers surrounding the plot represent angular directions of motion in the standard directions; numbers within the plot represent thresholds, expressed as the angular difference between two stimuli at threshold (in units of degrees).

2.3.2 The oblique effect in direction tuning width of motion adaptation

In order to characterize width of motion direction tuning in the visual system, we used the motion aftereffect (MAE; also known as the 'waterfall effect'), whereby prolonged viewing of a moving adapter stimulus causes subjects to have a perceptual bias towards perceiving motion in the opposite direction of the adapting stimulus [Anstis *et al.*, 1998]. We manipulated the directional variance of the adapting RDK by varying the standard deviation of the distribution from which dot directions were assigned (Figure 2.1B).

Initially, the adapting stimuli were presented at 100% coherence for 40 seconds. Each trial began with 4 seconds of top-up adaptation, followed by a second probe RDK with motion either in the adapting direction or in the opposite direction. Subjects discriminated the direction of motion in this probe stimulus (Figure 2.1C). We insured that the discrimination was made at threshold by adjusting the proportion of coherently moving dots in the probe stimulus based on a psychophysical staircase.

When coherence of the probe stimulus was very low, it appeared to be moving in the opposite direction from the direction of the adapting stimulus due to the MAE. However, when the coherence of the physical motion present in the stimulus was increased, the MAE was eventually overcome. The proportion of coherent dots in the post-adaptation probe stimulus was adjusted for each trial according to the subject's previous responses, and the threshold ($\sim 70\%$ of responses corresponding to perception of movement in the same direction as the adapting stimulus, in units of percent coherent dots) served as a measure of the strength of motion adaptation [Blake and Hiris, 1993]. For each subject, thresholds were computed for eight different adapting stimuli that spanned a range of directional variances. Additionally, each subject performed the task for two different adapter directions: the cardinal direction in which motion direction discrimination performance was best and the oblique direction in which motion direction discrimination performance was worst. In all but two subjects, this pair of directions corresponded to the directions in which the subjects achieved their best and worst direction discrimination performance across all eight directions.

When the standard deviation of the adapting stimulus was zero (all dots in the adapting RDK moved in the same direction), there was no significant difference in motion adaptation magnitude for cardinal and oblique directions (Figure 2.3A). However, when the standard deviation of the adapting stimulus was 22.5 degrees or more, a significant oblique effect was observed, with the oblique adapters resulting in stronger adaptation than cardinal adapters ($p < 0.05$). When the standard deviation was very large (90 degrees), substantially less adaptation was observed for either adapting direction. This MAE oblique effect can be represented as the difference between oblique and cardinal MAE strength (Figure 2.3B). These results indicate that the 'optimal width' for adaptation differs between the oblique and cardinal directions. For oblique directions, there was still significant adaptation even for adapting stimuli with widths of 22.5 and 45 degrees, while much less adaptation was observed for these widths for cardinal adapters.

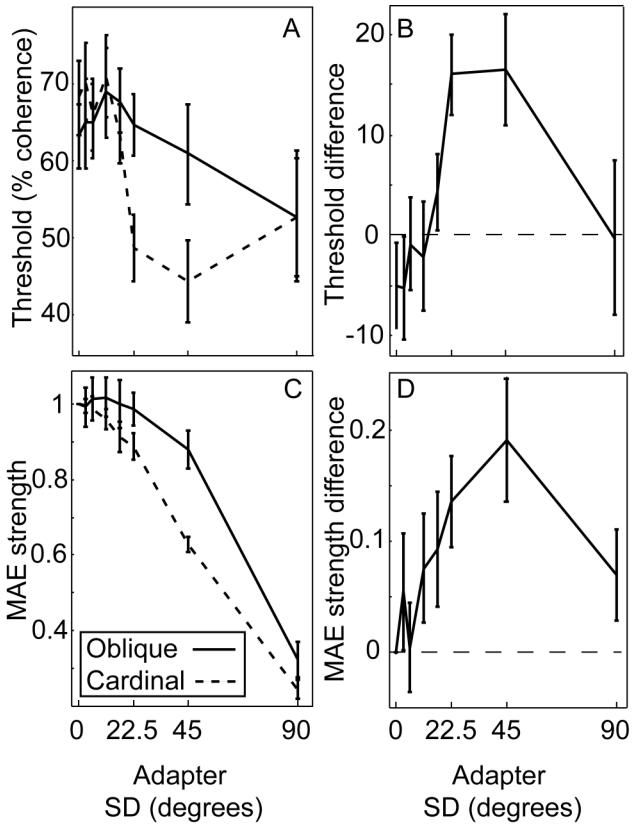

Figure 2.3: *The oblique effect for motion adaptation*. *A*: Average thresholds ($\pm 1 SEM$) for the MAE task are presented. The threshold in this task corresponded to the strength of the MAE for a given combination of adapter direction and standard deviation of motion directions. Solid line: oblique directions, dashed line: cardinal directions. *B*: Average difference ($\pm 1 SEM$) between MAE strength for oblique and cardinal directions. *C*: Model simulations of the MAE task provide an excellent fit of the experimental data. Average model thresholds (± 1 standard deviation for 10 repetitions of the simulation) are presented. *D*: The differences between the conditions in the model match the experimental data shown in panel *B*.

2.3.3 A model of encoding and decoding of motion direction in V1 and MT

To better understand the mechanisms underlying these psychophysical results, we constructed a computational model of encoding of motion stimuli in V1 and MT. The model contains two layers of units, one representing primary visual cortex (area V1), and the other representing area MT. There is a direct feedforward projection from the V1 layer to the MT layer. Each V1 unit has a profile of direction preference described by a circular Gaussian (a von Mises function, see 2.2). The profile of synaptic inputs to each MT unit from a group of V1 units is also described by a circular Gaussian. The model contains an anisotropy in the numbers of V1 units representing different directions and in the widths of tuning of units representing different directions [Li *et al.*, 2003]. MT units inherit this anisotropy through the synaptic connections between V1 and MT. Specifically, the width of tuning is relatively large in MT units tuned to oblique directions and relatively small in MT units tuned to cardinal directions. The model also applies untuned divisive normalization to the output of the units in the V1 layer: the output of each unit is passed through a static nonlinearity and then normalized by the summed activity of all the V1 units before being passed as input to the MT layer.

The activity in the population of MT units is decoded using a statistically optimal decoding based on a maximum likelihood algorithm [Jazayeri and Movshon, 2006]. This scheme takes into account the activity of all the cells in the MT layer and selects the direction of motion most likely to be present in the stimulus, given the activity of all the MT units, their tuning widths, and their preferred directions (see 2.2).

2.3.3.1 Modeling of motion direction discrimination

Direction discrimination relies on a comparison of the representation of motion direction in the two consecutive RDK presentations. Chance-level performance occurs when the difference between the two directions is below the resolution of the representation. In the task studied here, chance-level performance was 50%, as the task was a two alternative forced choice task (the subjects indicated whether the two stimuli had the same direction or different directions). In our computational model, we simulated motion direction discrimination by presenting the same stimulus twice. Because the spike rates produced by our model were stochastically drawn from Poisson distributions, the direction deemed to be the most likely by the decoding mechanism was different in two subsequent presentations of the same exact stimulus. The difference between the directions estimated to be the most likely by the decoding mechanism, $\Delta\theta$, is a measure of the fidelity of the representation of motion direction. When this procedure was repeated multiple times, a distribution of the estimated $\Delta\theta$ values was obtained. In order to fulfill the 50% chance performance level requirement, any $\Delta\theta$ smaller than the median of this distribution was considered to be a trial for which

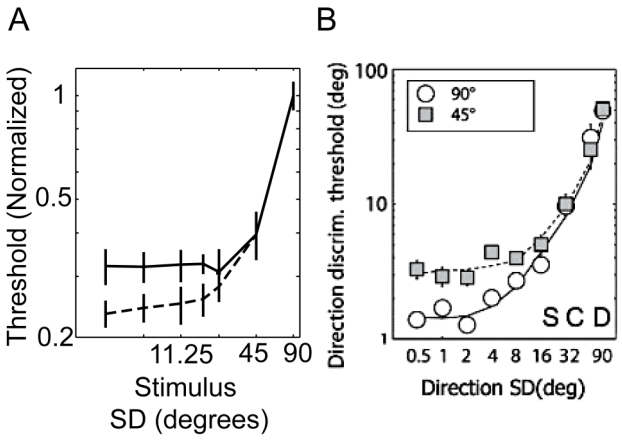

Figure 2.4: *Model simulation of motion direction discrimination. A*: Motion direction discrimination thresholds predicted by our model (± 1 standard deviation for 10 repetitions of the simulation) for cardinal (dashed) and oblique (solid) directions. When the stimuli contained only a single direction of motion (zero directional variance), discrimination thresholds were lower for cardinal than for oblique directions. This matches the experimental results presented in Figure 2. With increasing stimulus directional variance, the oblique effect diminished and eventually disappeared. *B*: The prediction of the model matches experimental results from a previous study (data from Dakin et al. 2005, copyright of ARVO, reproduced with permission). Thresholds in a motion discrimination task are presented for a single subject. Two directions, an oblique (grey squares) and a cardinal (white circles), are compared for different levels of direction standard deviation (SD, equivalent to the stimulus standard deviation in our model).

the subject's response would be that there was no difference between the two directions of motion. Hence, we took the median of this distribution to be an estimate of the direction discrimination threshold of the model.

For stimuli with no directional variance, there was a reliable difference in the thresholds predicted by the model for stimuli with oblique and cardinal directions (Figure 2.4A), replicating our psychophysical findings (Figure 2.2). However, as the directional variance of the stimuli increased, this oblique effect diminished, until at a standard deviation of 22.5-45 degrees, it disappeared. This pattern is strikingly similar to results reported by [Dakin *et al.*, 2005]. In this study, human observers were presented with oblique and cardinal motion patterns containing varying amounts of added directional noise (variance in the direction of motion assigned to each element in the pattern of moving stimuli). Consistent with our modeling results, Dakin et al. also observed an oblique effect in motion direction discrimination for low but not high levels of directional noise (Figure 2.4B).

2.3.3.2 Modeling of the MAE oblique effect

We simulated the motion adaptation experiment in the model by defining the strength of the MAE as the relative likelihood of the two antagonistic directions in the probe stimulus (the direction of the adapting stimulus and the opposite direction), given the profile of activity in the units [Gold and Shadlen, 2001].

This readout of the strength of the MAE from the population activity of the MT units produced an excellent fit to our psychophysical results from the motion adaptation task (Figure 2.3C). In particular, the model captured the substantial difference in adaptation strength between cardinal and oblique directions for intermediate adapter standard deviations and the minimal oblique effect for small and 90 degree standard deviations (Figure 2.3D).

2.3.3.3 Comparison between different decoding mechanisms

Decoding of the representations of stimuli in the model was performed by a maximum likelihood mechanism. There is psychophysical evidence that this is the mechanism underlying decoding of motion direction in humans [Jazayeri and Movshon, 2007]. However, other mechanisms have also been suggested for decoding of motion direction in area MT, including vector averaging [Nichols and Newsome, 2002] and winner-take-all [Salzman and Newsome, 1994; Zohary *et al.*, 1996; Nichols and Newsome, 2002]. We compared the abilities of these alternative decoding mechanisms to account for the psychophysical results. The encoding portion of the model was the same for all three decoding mechanisms, including the V1 directional anisotropy and the connectivity between V1 and MT, In vector averaging, each MT cell generates a vector pointing in the direction of that cell's preferred direction and proportional in length to that cell's firing rate. The direction of the average of these individual vectors is considered to be the direction coded by the population. The strength of the MAE was computed from the relative length of the component of the population vector for the direction opposite to the adapting direction.

The other decoding mechanism we considered is 'winner-take-all'. Here, the output of the model simply corresponds to the direction of motion preferred by the most active MT unit. The strength of the MAE was computed from the ratio between the activity in the unit which prefers the adapting direction and the activity in the unit which prefers the direction opposite to the adapting direction.

Figure 2.5 shows a comparison of the experimental results and the predictions of models based on the three decoding mechanisms. The maximum likelihood model best accounted for the width of tuning of motion adaptation as measured psychophysically (Figure 2.5A). In contrast, the vector-averaging model did not predict any difference in the MAE strength between oblique and cardinal directions except for an adapter standard deviation of 90 deg (Figure 2.5B). Also, the winner-take-all model predicted MAE strength differences only for adapting stimuli with a standard deviation of 45 degrees or greater (Figure 2.5C). The failure of the vector averaging and winner-take-all models to account for the psychophysical

results is probably due to the fact that both of these algorithms are necessarily invariant with regard to the tuning widths of the units in the model MT population. The population vector algorithm assigns equal weights to all the units in computing the population average, whereas the maximum-likelihood algorithm weighs evidence from some units more than others, depending on their tuning width. The winner-take-all model also does not utilize the anisotropies in the encoding of oblique and cardinal directions that are present in the population of MT units.

2.4 Discussion

2.4.1 A novel directional anisotropy in motion perception

Perception of motion is not isotropic. Motion in some directions is perceived more accurately than motion in other directions. We measured motion direction discrimination thresholds for eight directions and found lower discrimination thresholds for the cardinal directions (up/down, right/left) than for the oblique direction (off-cardinal diagonals). This result is a replication of previous findings ([Ball and Sekuler, 1982; Gros *et al.*, 1998; Dakin *et al.*, 2005].

In addition, we have demonstrated a novel anisotropy in motion perception following motion adaptation. The adapting stimuli were RDKs containing dots moving in different directions with a distribution of directions centered at either a cardinal or an oblique direction. Directional variance of the adapter was manipulated by changing the variance of the distribution of directions of the individual dots. The strength of adaptation was measured by determining the amount of coherent motion required to null the resulting motion aftereffect. For adapting stimuli with a small standard deviation of motion directions (0-17 degrees), there was no difference between the magnitude of the MAE induced in cardinal and oblique directions. However, for intermediate standard deviations (22.5-45 degrees), the MAE was significantly stronger for oblique than for cardinal directions. When the standard deviation of the adapting stimulus was very large (90 degrees), minimal adaptation occurred for both cardinal and oblique directions.

Our results suggest that the oblique effect in the MAE and in motion direction discrimination may reflect common neural mechanisms. Specifically, there may be directional anisotropies in the encoding and decoding of stimuli in the lower levels of the visual system that produce an oblique effect for both motion discrimination and motion adaptation.

One account of the MAE posits that it stems from a temporary imbalance in the activity levels of populations of cells representing opposite directions [Barlow and Hill, 1963]. Direction selective cells in area MT are known to change their response characteristics following adaptation to a moving stimulus [Petersen *et al.*, 1985]. Among other changes, the response of these cells to moving stimuli was reduced following adaptation. Additional evidence,

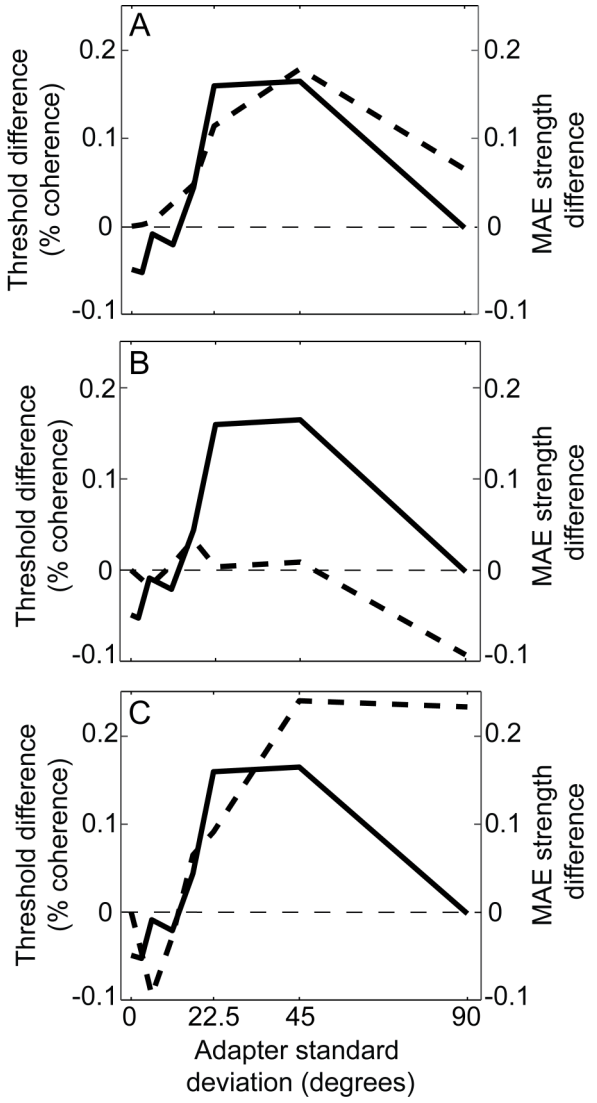

Figure 2.5: *Comparing different decoding mechanisms*. Model predictions of differences between cardinal and oblique adapting stimuli in the strength of the MAE (dashed lines) were compared to coherence threshold differences in the experimental results (solid line, same as the data presented in Figure 3B). Three decoding mechanisms were compared: *A* the statistically optimal maximum likelihood model, *B* the vector averaging model, and *C* the winner-take-all model. The maximum likelihood model clearly provided the best fit of the experimental data.

collected in the human brain using fMRI, also suggests that activity in area MT may be contributing to the MAE. Thus, presentation of an adapting stimulus caused direction-specific adaptation in human area MT+ and other visual cortical areas [Huk *et al.*, 2001]. However, there was no increase in the net activity measured in area MT+, suggesting that the MAE was induced not by a change in overall magnitude of activity in area MT+, but rather from differences in activity in different populations of direction-selective MT cells. Taken together, these results suggest that the sensation of motion relies on the distribution of activity within large populations of cells coding for direction, rather than an isolated change in the activity of a particular subset of direction-selective cells.

2.4.2 A model of encoding and decoding in V1 and MT

In order to explore possible mechanisms underlying our psychophysical results, we constructed a model of encoding of motion stimuli by populations of cells, based on the hierarchical organization of cortical areas V1 and MT. These areas contain neurons that are responsive to motion stimuli and selective for motion direction. Additionally, we implemented a decoding scheme based on a statistically optimal maximum likelihood decoding algorithm. Our results cannot be fully explained by reference to only the encoding or decoding aspects of our model, suggesting that an explanation of complex perceptual phenomena, such as the directional anisotropy in motion perception, requires an understanding of the mechanisms underlying both encoding and decoding of stimulus information. A similar approach has been successful in accounting for anisotropies in texture perception [Cohen and Zaidi, 2007].

2.4.2.1 Encoding

Area V1 contains direction-selective cells, and there are direct excitatory monosynaptic projections from area V1 to cells in area MT. Therefore, previous models of encoding by cells in area MT often contained a V1 layer with feedforward projections to a second MT layer [Simoncelli and Heeger, 1998; Rust *et al.*, 2006].

Another typical feature of these models is divisive normalization of the input to each cell in area MT by the summed V1 activity. Divisive normalization has been demonstrated physiologically in V1 [Carandini *et al.*, 1997]. Moreover, introducing divisive normalization in these models produces behaviors characteristic of MT. For example, the tuning of divisive normalization in the V1 to MT projection determines whether the MT cells integrate and average the pattern of motion of several different elements within their receptive field or whether they respond to each part of the pattern separately [Rust *et al.*, 2006].

In order to account for the directional anisotropy we observed in our behavioral experiments, we introduced a directional anisotropy in the encoding process, based on anisotropies revealed in physiological experiments in cat primary visual cortex [Li *et al.*, 2003]. There

were more V1 model units preferentially tuned to cardinal directions than units tuned to oblique directions, and the width of tuning of the units encoding cardinal directions was narrower than the width of the units encoding oblique directions. The model units representing MT cells then inherited the encoding anisotropy through the feedforward connections implemented in the model. Single-cell recordings from macaque area MT indicated no directional anisotropy in the population of recorded neurons [Churchland *et al.*, 2003], a results that is inconsistent with our model predictions. However, stimuli moving in cardinal directions activate a larger cortical area within owl monkey MT than stimuli moving in oblique directions, as measured using intrinsic signal optical imaging [Xu *et al.*, 2006]. Optical imaging has produced inconsistent results regarding the possible existence of a directional anisotropy in area V1, possibly related to differences across studies in the portion of the visual field representation that was imaged [Xu *et al.*, 2006; Xu *et al.*, 2007].

In order to understand the origins of these anisotropies, [Dakin *et al.*, 2005] performed an analysis of the statistics of motion energy present in movies recorded in natural environments. This analysis revealed greater motion energy in cardinal than oblique directions during movement through natural environments. If the visual system is able to learn these statistical regularities, the anisotropy in motion perception may be a consequence of experience. Indeed, the oblique effect can be partially abolished with training [Ball and Sekuler, 1982]. However, comparisons between subjects from different ethnic groups, living in similar environments, indicated slight differences in the oblique effect in sensitivity to different orientations [Timney and Muir, 1976; Ross and Woodhouse, 1979]. This suggests that there may be a genetic component of at least some types of oblique effect. Thus, anisotropies in visual inputs could possibly generate perceptual and neural anisotropies though natural selection as well as through experience-dependent development. The encoding of the motion aftereffect was implemented in our model by applying activity-dependent adaptation to the MT cells. Consistent with the physiologically measured reduction in response amplitude of MT cells following exposure to motion in their preferred direction [Petersen *et al.*, 1985], we assumed that MT cells integrate information about ongoing activity in the V1 cells through their synaptic connections. Specifically, the cells in our model that responded most vigorously to the adapting stimulus were the cells that responded the least to the post-adaptation probe stimulus.

2.4.2.2 Decoding

Our model implements an optimal decoding scheme based on the activity of the population of units representing MT neurons. This scheme determined the direction of motion that was most likely for each stimulus, given the population of MT neurons that responded to that stimulus. In our implementation of the model, the likelihood of a direction was weighted not only by the activity of the units representing that direction, but also by the relative

reliability of the cells' responses, as reflected in the relative width of their tuning.

This kind of algorithm has been shown to be neurally plausible. A network of realistic neurons can implement maximum likelihood decoding [Deneve *et al.*, 1999; Jazayeri and Movshon, 2006], and neurons in higher-level visual areas, reading out the information from area MT, modulate their activity pattern in a way which is consistent with this algorithm [Gold and Shadlen, 2001]. Also, human observers have been found to act near-optimally when integrating information in their sensory environment [Ernst and Banks, 2002; Battaglia *et al.*, 2003]. These findings suggest that decoding of information that is represented at an intermediate level of processing, such as area MT, may proceed in a statistically optimal fashion.

We tested our model of decoding by comparing the optimal maximum likelihood strategy to other decoding algorithms. Specifically, we tested two decoding schemes which have been proposed for MT neurons: a vector averaging algorithm [Nichols and Newsome, 2002] and a winner-take-all algorithm [Salzman and Newsome, 1994; Zohary *et al.*, 1996]. The best description of our data is clearly provided by the optimal maximum likelihood decoding algorithm. A recent study has shown that different decoding strategies may be used in solving different tasks, even if the strategies employ the same decoding algorithm. A maximum likelihood algorithm accounted for subject's performance for both coarse and fine direction discriminations, but slight biases in the subject's performance revealed that information about coarse and fine discriminations was derived from different populations of neurons [Jazayeri and Movshon, 2007]. Furthermore, we cannot exclude the possibility that, under particular circumstances, decoding schemes other than the maximum likelihood mechanism may be utilized. For example, when integrating visual and auditory information in a target localization task, subjects probably use a hybrid decoding strategy. Specifically, they combine the maximum likelihood decoding algorithm with a tendency to rely on visual information rather than on auditory information, which is a form of the winner-take-all model [Battaglia *et al.*, 2003].

In addition, implementations of the maximum likelihood algorithm in models of neural networks require multiple iterations to converge [Deneve *et al.*, 1999]. Thus, the implementation of this algorithm in the brain may be more time consuming than implementation of the vector averaging or winner-take-all decoding algorithms and may require more information about the tuning properties of the encoding cells than these alternative algorithms [Oram *et al.*, 1998]. Thus, the brain may employ different decoding schemes, depending on the task being performed and on the information available.

2.4.3 The effect of stimulus directional variance on the oblique effect in direction discrimination

In addition to accounting for our psychophysical results, our model also produces novel predictions. Specifically, as the directional variance of the stimulus increases, absolute thresh-

olds in the motion direction discrimination task should also increase, but the directional anisotropy of these thresholds (the difference in thresholds for cardinal and oblique stimuli) should decrease. This prediction was not tested in our behavioral experiments, as subjects performed the direction discrimination task only in the zero directional variance condition.

However, this prediction has been tested in a previous study [Dakin *et al.*, 2005]. Human observers performed a motion direction discrimination task in both cardinal and oblique directions, and the directional variance in the stimulus was manipulated. Two results were obtained in Dakin et al.'s study that are pertinent to this discussion: *1* as the directional variance of the stimulus increased, the threshold of direction discrimination increased. That is, the task became more difficult. *2* As the directional variance of the stimulus increased, the oblique effect decreased. That is, the difference between direction discrimination thresholds in the oblique and the cardinal directions became smaller. At sufficiently large directional variances, the oblique effect was completely abolished. Both of these results are captured in the results of the simulations we conducted.

Despite the match between our model and the empirical results obtained by Dakin et al., there are differences in interpretation between our study and that of Dakin et al. They interpreted their results within the framework of an equivalent noise model, which assumes that direction discrimination thresholds reflect the sum of the noise that exists in the stimulus (the variance in the motion directions of the elements) and the internal noise (in the representation of the stimulus by the visual system). In contrast, our computational modeling results suggest that the relationship between variance of motion direction in the stimulus and direction anisotropy in motion direction discrimination thresholds can be accounted for by a combination of directional anisotropies in stimulus encoding and a maximum likelihood decoding strategy. Both the equivalent noise model of Dakin et al. and our computational model of V1 and MT provide an excellent description of the behavioral results (Figure 2.4).

However, the two models make different predictions regarding the existence of physiological directional anisotropies in area MT. Our model posits that an oblique effect should be present in the tuning of MT neurons (inherited from the V1 neurons), while Dakin et al. conclude that no such oblique effect should exist in MT. Their interpretation relies on the assumption that when the standard deviation of the directions of motion in the stimulus is small, there is no need to integrate over many different elements, and the reliability of the representation will therefore be limited by the fidelity of the responses of cells in V1. When the standard deviation of the stimulus is larger, cells in MT must integrate the directions of motion of all the elements within their receptive fields. Thus, Dakin et al. reason that when integration over many elements is required in order to determine the direction of motion of the pattern, the threshold results from the activity of MT cells. However, more recent physiological recordings have shown that MT neurons only integrate elements within their receptive fields when these elements spatially overlap [Majaj *et al.*, 2007].

2.4.4 Task dependence of the oblique effect for motion

Our model posits that the behavioral oblique effect is a consequence of an anisotropy in the primary representation of motion stimuli and of the decoding mechanism applied to this representation. If the oblique effect is indeed a consequence of the primary representation of the stimulus, it should also be present for other tasks involving motion perception. However, directional anisotropies have not been found for detection of coherent motion in a field of incoherently moving dots [Gros *et al.*, 1998] or for speed discrimination [Gros *et al.*, 1998; Westheimer, 2003]. One interpretation of the lack of oblique effect in these tasks is that encoding of the motion stimulus by the visual system is isotropic, and the anisotropy only results from decoding in higher-level areas [Westheimer, 2003].

We have not simulated either motion detection or speed discrimination tasks in the characterization of our model. However, the model is constructed such that the total firing rate of the population of MT cells is invariant to motion direction. This invariance is consistent with the lack of directional anisotropy in tasks requiring detection of coherent motion. Simulations of these tasks will be the topic of further studies of the model.

2.4.5 Summary and conclusions

We have described a novel oblique effect in motion perception in which the tuning width of adaptation is different for oblique and cardinal directions. In addition, we constructed a computational model of encoding and decoding of motion direction information in the visual system. Our model accounts for four distinct psychophysical findings: *1* an oblique effect in the strength of motion adaptation (Figures 2.3 and 2.4), *2* an oblique effect in the width of direction tuning of motion adaptation (Figures 2.3), *3* an oblique effect in motion direction discrimination thresholds (Figure 2.2 and the points in Figure 2.4A corresponding to zero directional variance in the stimulus), and *4* the directional tuning of the oblique effect in motion direction discrimination, originally described in [Dakin *et al.*, 2005] (Figure 2.4). The model accounts for these findings only when a specific combination of encoding anisotropies and decoding mechanism is implemented. On the encoding side, more V1 units represent cardinal directions than oblique directions, and the units coding for cardinal directions are more narrowly tuned than those coding oblique directions. These directional anisotropies are inherited by MT units through the pattern of connectivity between V1 and MT. On the decoding side, a statistically optimal maximum likelihood decoding algorithm is used to read out the information from the population of MT units. These modeling results emphasize the significance of addressing both encoding and decoding of stimulus information when describing complex perceptual phenomena.

Chapter 3

Cholinergic enhancement augments magnitude and specificity of visual perceptual learning in healthy humans

3.1 Introduction

Learning through experience underlies our ability to adapt to novel tasks and unfamiliar environments. However, these changes must be regulated so that relevant aspects of the environment are selectively encoded. The neurotransmitter acetylcholine (ACh) has been suggested to play an important role in regulating learning by enhancing the responses of sensory neurons to behaviorally relevant stimuli [Sarter *et al.*, 2005]. Cholinergic neurons in the basal forebrain project widely to cortex, where they increase ACh release when animals are performing a task requiring sustained attention [Arnold *et al.*, 2002]. In addition, application of ACh in cortex induces persistent changes in neuronal tuning [Greuel *et al.*, 1988], and pairing of basal forebrain electrical stimulation with presentation of a sensory stimulus causes changes in cortical tuning that are similar to those observed when the animal performs a task on the presented stimulus [Kilgard and Merzenich, 1998]. In humans, pharmacological reduction of cholinergic transmission has been shown to prevent learning-dependent changes in fMRI responses [Thiel *et al.*, 2002].

Cholinesterase inhibitors such as physostigmine and donepezil are commonly prescribed drug treatments for Alzheimers disease, a disease characterized by a selective degeneration of cholinergic neurons in the basal forebrain [Whitehouse *et al.*, 1982]. This class of drugs inhibits the enzyme that breaks down ACh in the synaptic cleft, thereby prolonging the effects of endogenously released ACh. Some studies have reported that cholinesterase inhibitors significantly improve measures of cognitive function and of quality of life in patients using them [Mohs *et al.*, 2001], but a controversy about the utility of their administration still exists [Courtney *et al.*, 2004]. It would therefore be beneficial to understand the specific

aspects of cognition and behavioral performance that are enhanced by increases in synaptic ACh. A previous study has shown that administration of physostigmine to healthy humans enhances the behavioural effects of visual spatial attention [Bentley *et al.*, 2004], but another study reported no effects on performance in tasks requiring visual spatial attention[Bentley *et al.*, 2003]. Also, administration of physostigmine [Davis *et al.*, 1978], as well as donepezil [Grön *et al.*, 2005], can improve long-term retention of memorized items, but this effect has also not always been found [Nathan *et al.*, 2001]. In summary, though these results suggest that this class of drugs may benefit cognitive function, the exact nature of these benefits and their neural mechanisms are still not fully understood.

We examined the effects of cholinergic enhancement with donepezil (trade name: Aricept) on perceptual learning of a motion direction discrimination task. Perceptual learning is a pervasive improvement in performance of a perceptual task with training. This improvement is often found to be stimulus-specific. That is, the effects of learning do not completely generalize beyond the specific stimulus characteristics presented during training. Specificity of visual perceptual learning has been reported for various characteristics of the training stimulus, including location in the visual field [Dill, 2002], color and spatial frequency [Fiorentini, 2002], eye of training [Fahle *et al.*, 1995], and orientation of elements in the display [Ahissar and Hochstein, 1997]. When trained on a motion direction discrimination like the one used here (Figure 3.1A), subjects performance improved for the direction of motion on which they trained, but this improvement did not generalize to other motion direction [Ball and Sekuler, 1987]. The specificity of perceptual learning is often interpreted as a change in coding in neurons specifically tuned to the stimulus characteristics for which specificity of learning exists. This idea receives support from physiological findings in humans [Furmanski *et al.*, 2004] and other primates [Schoups *et al.*, 2001; Ghose *et al.*, 2002; Yang and Maunsell, 2004], where stimulus-specific effects of perceptual learning have been described in area V1 and other early visual cortical areas containing neurons that are tuned to the stimulus characteristics employed during training.

3.2 Methods

3.2.1 Subjects

Twelve subjects (seven female; mean age: 23 ± 6) passed a health screen and provided informed consent. Tobacco smokers were excluded from participation. All subjects had normal or corrected-to-normal vision.

3.2.2 Task

In each trial, subjects reported whether two sequentially presented random dot kinematograms (RDKs) were moving in the same or different directions [Ball and Sekuler, 1987; Rokem and

Silver, 2009] (Figure 3.1A). The angular difference between the stimuli was adjusted according to a Quest psychophysical staircase, converging on 70% correct performance, and each threshold was estimated from all trials in a given staircase [Watson and Pelli, 1983]. The RDKs, created using the Psychophysics Toolbox [Brainard, 1997; Pelli, 1997], covered an annulus subtending 1.5-3.1 deg of visual angle around the fixation point (Figure 3.1B). The radius of each dot was 0.03 deg, and the dot density was 17 $dots/deg^2$. The dots were moving at a speed of 8 deg/sec, and each dot moved continuously for two monitor frames (approximately 24 msec at the 85 Hz refresh rate used) before being reassigned to another random location within the annulus. Two quadrants of the RDK, located on opposite sides of the fixation point, contained 100% coherent motion. The remaining quadrants contained 0% coherent motion.

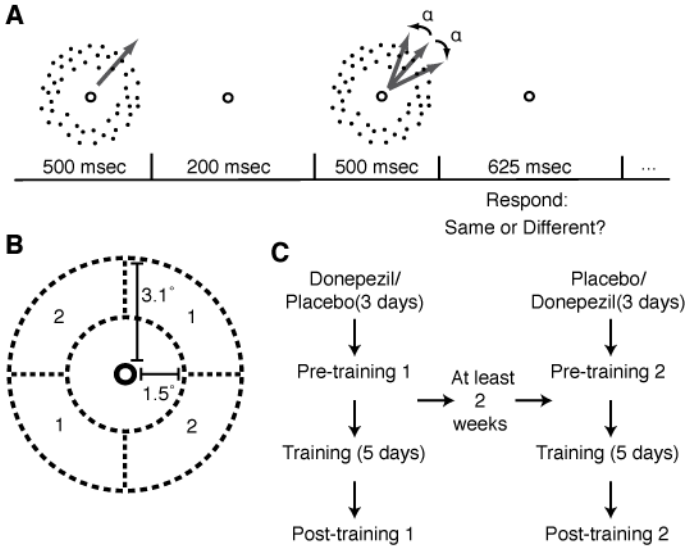

Figure 3.1: *Experimental procedure*. *A*, Task description. In each trial, two fields of coherently moving dots were sequentially presented. The two fields contained either the same or slightly different directions of motion. *B* Stimulus configuration. During training, coherent motion was presented in one of two pairs of spatial locations (1 or 2) and was always in the trained direction. *C* Training procedure. Subjects participated in two courses of training. Donepezil or placebo was administered beginning three days before the pre-training measurement and daily throughout training and the post-training measurement.

3.2.3 Procedure

Subjects participated in two courses of training (Figure 3.1C). Each course was preceded by three days of donepezil or placebo administration, bringing drug plasma levels to within the steady-state range (the half-life of donepezil in the human body is approximately 80 hours [Rogers *et al.*, 1998]), and drug/placebo administration continued daily throughout training and the post-training assessment. Before and after training, subjects performed the task in both pairs of locations and for eight different directions of motion. For each course of training, subjects repeatedly performed the task for a particular stimulus with coherent motion in one direction and in one of the two possible pairs of locations (Figure 3.1B). Human subjects exhibit differences in performance of this task for oblique and cardinal directions of motion [Ball and Sekuler, 1987; Rokem and Silver, 2009]. We therefore used only oblique direction for training. During training, participants performed 1000 trials every day. Subjects underwent five days of training, except for one subject who trained for six days in both the placebo and donepezil conditions. Another subject did not perform a post-training assessment under placebo in the untrained locations, and these values were entered into the analysis as missing values. At least two weeks passed between the two courses of training, allowing for donepezil, if present, to be completely eliminated.

3.2.4 Analysis

Differences in task performance were evaluated using a mixed-model ANOVA, with drug condition (donepezil vs. placebo), training (pre- vs. post-), visual field location (trained vs. untrained), and direction of motion (5 levels: 0, 45, 90, 135, and 180 degrees offset from trained direction) as within-subject factors. In order to discount the effect of order of drug/placebo administration on thresholds (which was orthogonal to the effect of the drug, due to the counterbalance), statistical testing was performed with order of drug administration as a between-subjects covariate. In addition, planned comparisons between conditions were conducted in order to investigate specific hypotheses [Kirk, 1968].

For each subject and each condition, percent learning was calculated using the following formula:

$$\%learning = 100 \cdot (1 - \frac{threshold(post)}{threshold(pre)}) \tag{3.1}$$

In order to test whether learning was significantly faster under donepezil than under placebo, the average percent learning in each daily session was calculated for each subject and then averaged across subjects. A single-parameter model was fit to the progression of learning:

$$\%learning(session) = 100 \cdot (1 - e^{\tau \cdot session}) \tag{3.2}$$

where τ is the parameter that quantifies the rate of learning. Since the data did not allow for a reliable model fit on the single subject level, a jackknife procedure was employed [Efron and Tibshirani, 1993]. The model was fit to twelve resamples from the data. For each resample, the data from one subject were omitted, and the learning curves from the remaining eleven subjects were averaged. The model was then fit to this average learning curve. This produced twelve different values of learning rate (τ) for each condition. The values of the learning rates were then compared across the jackknife samples. Average learning rates were found to be greater in the donepezil condition, 0.04 ± 0.008, than in the placebo condition, 0.02 ± 0.005. In order to estimate the statistical significance of this difference, a non-parametric permutation test was used: 10,000 surrogate samples were created by randomly recoding the condition from which each value of the learning rate was taken (donepezil or placebo). This was done independently for each jackknife sample. Thus, the distribution of the differences between the means of these recoded distributions corresponds to that expected for the null hypothesis (no effect of donepezil on learning rate). However, the mean difference between the actual jackknife distributions (donepezil and placebo) was larger than 95% of the randomly recoded samples created in this condition, indicating that the probability of the measured differences between donepezil and placebo learning rates occurring by chance is smaller than 0.05.

3.3 Results

In each trial, subjects reported whether two fields of moving dots, presented sequentially, were moving in the same direction [Ball and Sekuler, 1987] (Figure 3.1). The discrimination threshold was defined as the minimal angular separation between the two stimuli that allowed a difference in motion direction to be reliably detected. Thresholds were measured in two different visual field locations and eight different motion directions before and after each course of training. Subjects trained on this task for an hour each day over the course of five days.

One of the visual field locations and one direction of motion were selected to be the training stimulus, and this stimulus was the only one presented during training. Each subject completed two courses of training: once while ingesting a pill containing 5 mg of donepezil before every training session, and once while an inactive placebo was administered. Drug administration was double-blind, and the order of drug and placebo administration was counter-balanced between subjects. Since training in this task is specific for visual field location and motion direction [Ball and Sekuler, 1987], the effects of the two courses of training were separately assessed in each subject by training in two different visual field locations and on opposite motion directions.

Perceptual learning resulted in an improvement in performance for the trained direction of motion and visual field location (Figure 3.2). However, the main effect of training (pre-

vs. post-training thresholds, across all directions of motion and both locations, as assessed by the significance of the training factor in the ANOVA) was not significant ($F_{1,9} = 0.53$, $p > 0.5$), demonstrating the specificity of learning for the training stimulus. Administration of donepezil had an overall facilitatory effect on learning, as evidenced by a significant interaction of drug and training in the ANOVA ($F_{1,9} = 5.89$, $p < 0.05$).

Training decreased discrimination thresholds for the training stimulus (Figure 3.2). This decrease was significant both when subjects were taking donepezil, with an average improvement of 6.2±2.1 deg (planned comparison, $t_{36} = 6.81$, $p < 0.05$), and under placebo, 2.2±0.8 deg (planned comparison, $t_{36} = 2.42$, $p < 0.05$). However, the improvement in performance in the trained condition during donepezil administration was significantly larger than the improvement under placebo (planned comparison, $t_{36} = 3.1$, $p < 0.05$).

In addition to enhancing the amount of learning, donepezil also increased its selectivity. Direction specificity of perceptual learning was assessed by subtracting the improvement in performance in the untrained directions of motion (in the trained location) from the improvement in the trained direction (in the trained location). This measure of selectivity was larger for donepezil (4.0 ± 1.2 deg) than for placebo (1.4 ± 1.1 deg; planned comparison, $t_{36} = 2.82$, $p < 0.05$). A similar measure of location selectivity was also calculated, and the difference in improvement in the trained visual field location (in the trained direction) and improvement in the untrained locations (in the trained direction) was also significantly larger under donepezil (3.0±1.2 deg) relative to placebo (−1.2±1.0 deg; planned comparison, $t_{36} = 2.97$, $p < 0.05$).

Comparisons of raw threshold values are sensitive to between-subject performance differences and to the effects of the drug on overall performance (individual subject data are presented in 3.4). Therefore, we calculated the percent learning for each subject relative to that subject's pre-training performance (Figure 3.3). Percent learning in the trained condition was greater for donepezil than for placebo (planned comparison, $t_{36} = 2.5$, $p < 0.05$), demonstrating that the beneficial effects of donepezil on learning were not due to the drugs effects on overall performance.

Nevertheless, in addition to donepezils beneficial effects on perceptual learning, there was an overall deleterious effect of the drug on task performance ($F_{1,9} = 12.76$, $p < 0.05$, combining all directions and both locations, as assessed by the significance of the drug factor in the ANOVA), which may stem from non-specific effects of cholinergic enhancement (see 3.4. In particular, pre-training thresholds for the direction of motion and visual field location used for training were numerically higher under donepezil (13.3 ± 2.4 deg) than under placebo (10.7 ± 0.8 deg), raising the possibility that the drug effect on the magnitude of learning was due to this drug/placebo difference in pre-training thresholds. However, this difference in pre-training thresholds was not statistically significant ($t_{11} = 1.17$, $p > 0.05$). On the other hand, post-training thresholds for the training stimulus were significantly lower under donepezil (7.2±0.6 deg) than under placebo (8.5±0.5 deg, $t_{11} = 2.81$, $p < 0.05$). There were no significant effects of the drug on thresholds for any other combination of location and

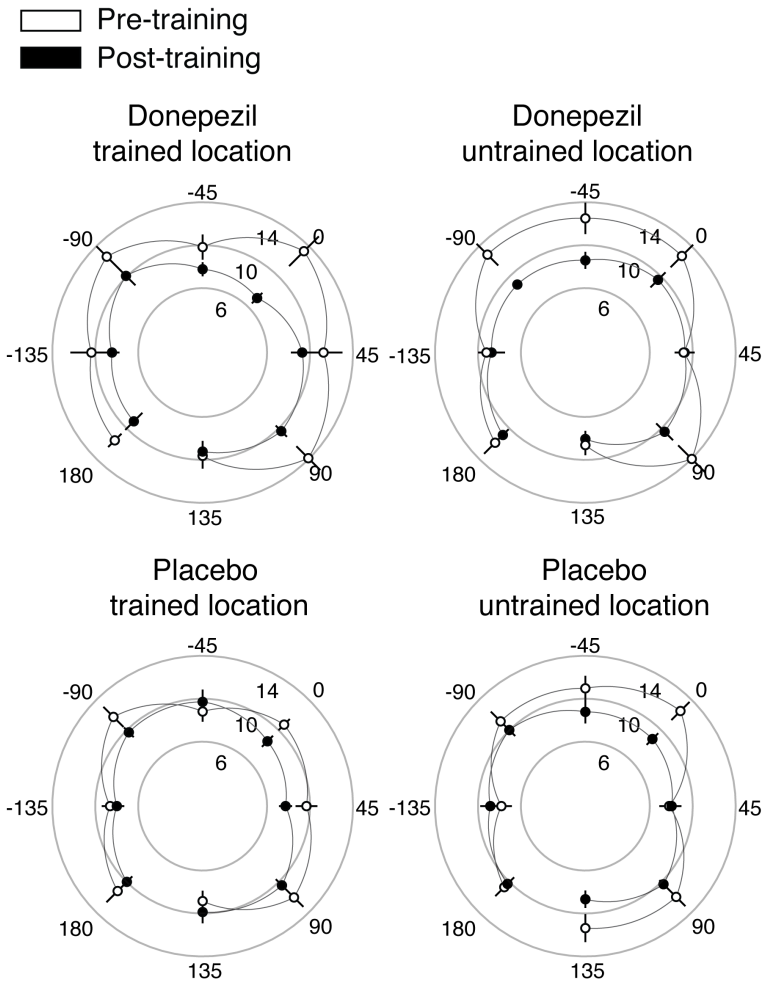

Figure 3.2: *Donepezil increases magnitude of perceptual learning* Each plot displays task performance for different directions of motion, where 0 degrees corresponds to the direction used for training. There was a significant improvement in performance for the training stimulus (trained direction and visual field location), and this improvement was substantially larger under donepezil than under placebo. Error bars denote SEM.

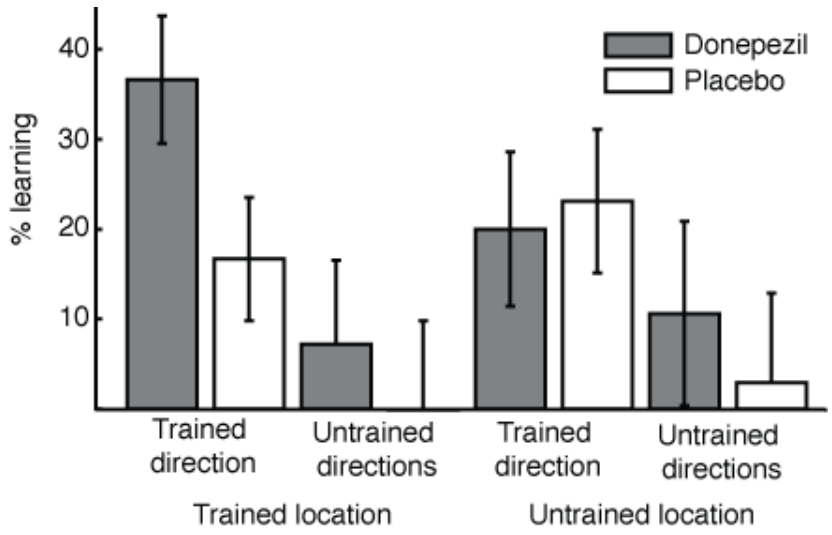

Figure 3.3: *Donepezil increased magnitude and specificity of perceptual learning.* Percent learning was significantly larger under donepezil in the trained condition. Location specificity is the difference between percent learning in the trained visual field location (in the trained direction) and percent learning in the untrained location (in the trained direction). Direction specificity is the difference between percent learning in the trained direction (in the trained location) and percent learning in the untrained directions (in the trained location). Donepezil increased both of these measures of selectivity of learning. Error bars denote SEM

direction, either before or after training. The presence of significant drug effects on discriminability of the training stimulus in the post- but not the pre-training condition demonstrates that the beneficial effects of cholinergic enhancement on the magnitude of learning are not due to general effects of the drug on task performance, as this would presumably have affected both pre- and post-training thresholds.

Further evidence that the effects of donepezil on overall performance do not account for the effect of donepezil on perceptual learning comes from excluding one subject whose pre-training threshold for the training stimulus while taking donepezil was 34 degrees (see 3.4 for single subject data). This value was 2.7 standard deviations above the mean pre-training donepezil threshold for the training stimulus. This outlier subject accounts for most of the drug effect on mean pre-training threshold but is not responsible for the pattern of drug effects on learning. When this subjects data were removed from the sample, the donepezil/placebo difference in pre-training thresholds was reduced (donepezil: 11.5 ± 1.5 deg; placebo: 10.5 ± 0.8 deg, $t_{10} = 0.6$, $p > 0.5$), while the difference in post-training thresholds was still statistically significant (donepezil: 7.1 ± 0.7 deg; placebo: 8.6 ± 0.6 deg, $t_{10} = 2.7$, $p < 0.05$).

We also conducted the statistical analysis of donepezils effects on learning while excluding this subjects data from the sample. The interaction of drug and training was still present ($F_{1,8} = 6.64$, $p < 0.05$), as was the effect of donepezil on the magnitude of perceptual learning (donepezil: $33 \pm 6\%$, placebo: $15 \pm 8\%$; $t_{32} = 2.05$, $p < 0.05$). In addition, donepezil still increased the location specificity ($t_{32} = 2.21$, $p < 0.05$) and direction specificity ($t_{32} = 2.34$, $p < 0.05$) of learning. Finally, although the outlier subject had a very large donepezil pre-training threshold for the training stimulus, three subjects exhibited greater effects of donepezil on learning (difference between percent learning under donepezil and percent learning under placebo; see Figure 3.4B for single subject values). We conclude that the worse pre-training performance under donepezil cannot account for the increases in magnitude and specificity of perceptual learning under donepezil.

Perceptual learning is often found to be variable between subjects [Mukai *et al.*, 2007]. In our study, subjects also differed in the magnitude of the effect of donepezil on perceptual learning. Figure 3.4 relates pre- and post-training thresholds for each participant separately for placebo and donepezil. We examined a number of factors to determine whether they predicted either the magnitude of the effect of the drug on learning or the amount of learning under donepezil: *1* the pre-training thresholds, which correspond to baseline motion direction discrimination performance, *2* percent learning under placebo, which represents the amount of learning in the absence of pharmacological manipulation, and *3* average percent learning (average of placebo and donepezil conditions), which serves as an unbiased estimate of learning for a given subject.

Pre-training performance did not predict the magnitude of the effect of donepezil on learning: the correlation between pre-training thresholds (averaged between drug and placebo conditions) and the drug effect on percent learning (in the trained condition, defined as the

difference between percent learning under donepezil and percent learning under placebo) was not significant ($r^2 = 0.09$, $p = 0.35$). We also correlated percent learning under placebo with percent learning under donepezil and found no significant relationship between these two measures ($r^2 = 0.001$, $p = 0.96$) (Figure 3.4B). This indicates that the amount of learning for a given subject under placebo does not predict how much learning occurs for that subject during cholinergic enhancement. In addition, there was no correlation between the overall amount of learning for a given subject (average of percent learning in donepezil and placebo conditions) and the magnitude of the effect of donepezil on learning (difference between percent learning in donepezil and placebo conditions) ($r^2 = 0.01$, $p = 0.77$).

In order to determine whether the increase in the magnitude of learning under donepezil was a consequence of more rapid learning, we examined the progression of learning in the trained location and direction for both donepezil and placebo (Figure 3.5). A single-parameter model of learning was fit to the data (see Supplementary Methods), and a jackknife procedure [Efron and Tibshirani, 1993] was employed to estimate the rate and variability of learning under placebo and donepezil. Statistical significance of the effect of cholinergic enhancement on learning rate was calculated using a non-parametric permutation test (see 3.2). This test demonstrated that learning was significantly more rapid under donepezil ($p < 0.05$).

3.4 Discussion

We have shown that cholinergic enhancement with donepezil during perceptual learning of a visual motion direction discrimination task enhances the magnitude and specificity of perceptual learning in healthy humans. This enhanced selectivity of learning, combined with previous studies demonstrating an increase in neuronal selectivity following cholinergic enhancement [Goard and Dan, 2009; Furey *et al.*, 2000; Silver *et al.*, 2008], suggests a possible mechanism by which ACh augments plasticity and tuning in populations of neurons that encode behaviourally-relevant stimulus features.

Other studies in animals have shown that ACh increases transmission at feedforward thalamocortical synapses relative to lateral intracortical connections [Giocomo and Hasselmo, 2007]. ACh reduces the spatial spread of excitatory activity following electrical stimulation of rat visual cortical slice s[Kimura *et al.*, 1999] and decreases the preferred stimulus length of cells in marmoset area V1 [Roberts *et al.*, 2005]. In addition, electrical stimulation of the basal forebrain results in a more reliable representation of the stimulus in visual cortical neurons [Goard and Dan, 2009]. In humans, donepezil reduces the spatial spread of excitatory fMRI visual responses in early visual cortex, consistent with a reduction in excitatory receptive field size of visual cortical neurons [Silver *et al.*, 2008], and physostigmine increases the selectivity of responses in visual association cortex [Furey *et al.*, 2000]. Our findings suggest that during perceptual learning, these increases in neural selectivity by ACh may

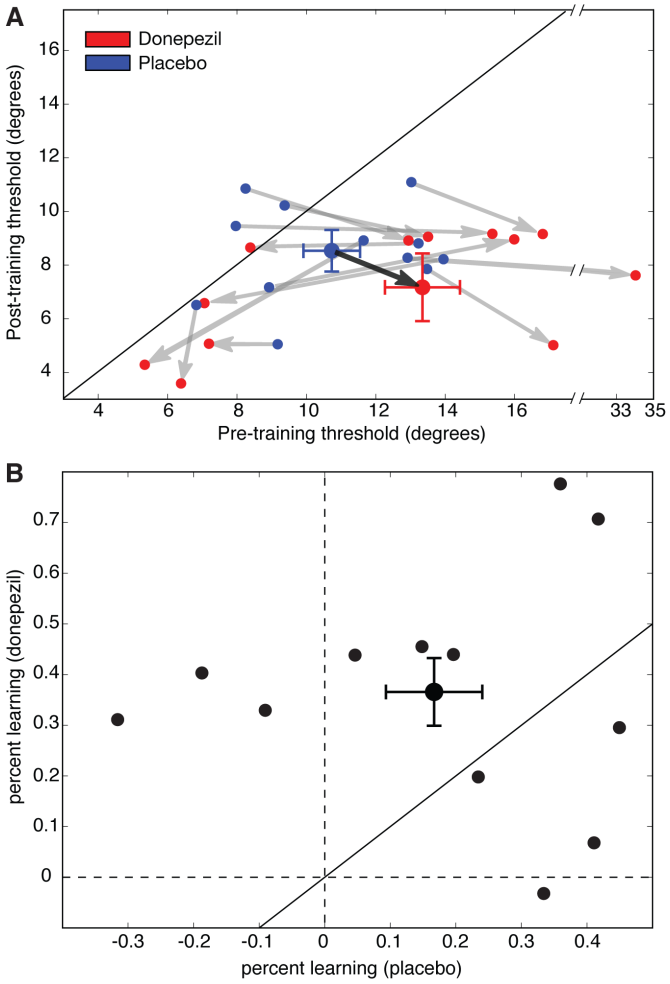

Figure 3.4: *Individual differences in perceptual learning and its modulation by donepezil. A* pre- and post-training thresholds for placebo and donepezil. Each subjects behavioral performance is displayed as a pair of points (blue = placebo, red = donepezil) connected by an arrow. The distance of each point from the equality (solid black) line indicates how much learning (change from pre- to post-learning threshold) occurred in that condition. The direction of the arrow connecting the placebo and donepezil points for a given subject indicates the effect of the drug on learning. When this arrow points away from the equality line (rightwards and downwards), this indicates that donepezil increased the magnitude of learning. Large points are the group averages with SEM error bars. *B* comparison of percent learning under donepezil and placebo. The distance of each point from the equality (solid black) line indexes differences in the amount of learning under placebo and donepezil. Points above the line represent subjects who exhibited more learning under donepezil than under placebo. The large point represents the group average with SEM error bars.

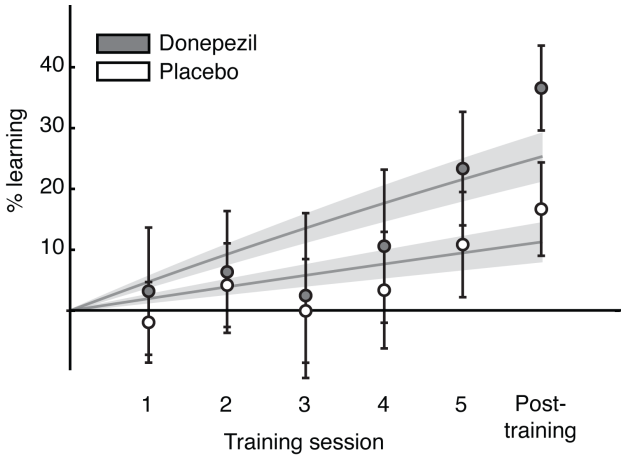

Figure 3.5: *Donepezil increases rate of perceptual learning*. Percent learning of the training stimulus is presented as a function of training session. Training under donepezil (filled markers) proceeded at a more rapid rate than training under placebo (empty markers). Learning rates were computed by fitting a single-parameter model of learning to the data (gray continuous lines, where the shaded area is the standard deviation derived from a jackknife estimate)

enhance learning-dependent changes in tuning of the neurons that encode task-relevant stimuli. This is consistent with previous models of the role of the cholinergic system in learning and memory [Sarter *et al.*, 2003].

One factor that could be mediating the effects of cholinergic transmission on learning is visual attention. Attention has been found to play an important facilitatory role in some types of perceptual learning [Ahissar and Hochstein, 1993], and ACh is thought to modulate allocation of attention [Sarter *et al.*, 2005]. We have also found that cholinergic enhancement with donepezil increases the effects of voluntary visual spatial attention in a visual discrimination task (see Chapter 4). In the present study, donepezil may have facilitated processing of the training stimulus through enhanced allocation of voluntary attention to this stimulus, thereby augmenting perceptual learning.

It is important to note that perceptual learning does not always require attention to be directed to the stimulus and that learning can occur even in the absence of conscious perception of the stimulus. Watanabe et al. [Watanabe *et al.*, 2001] instructed participants to perform a difficult sensory judgment in the center of the visual field while a task-irrelevant motion stimulus was presented in the peripheral visual field. Although the amount of coherent motion in the peripheral stimulus was below the detection threshold, subjects improved in performance of a motion discrimination task for the direction of motion contained in the peripheral stimulus, and the learning was specific to that direction of motion. However, even for this kind of task-irrelevant perceptual learning, training was still affected by attention, in

that learning for the subthreshold stimuli appearing in peripheral vision occurred only when the peripheral stimulus was presented at the same time that the target appeared in central vision [Seitz and Watanabe, 2003]. Thus, simultaneous presentation of the task-irrelevant stimulus and engagement of attention are required to facilitate perceptual plasticity. Furthermore, another study [Nishina *et al.*, 2007] demonstrated that task-irrelevant perceptual learning depends on the relative locations of the task-irrelevant and task-relevant stimuli. Task-irrelevant perceptual learning was demonstrated for stimuli that were near the task-relevant stimulus but was not observed for stimuli that were farther away (6.6 degrees of visual angle) from the attended stimulus. Acetylcholine is released in cortex when animals are performing a task requiring sustained attention [Arnold *et al.*, 2002]. A recent study showed that ACh can be released in frontal cortex in a transient and spatially-specific manner and that this transient release of ACh increases the probability of stimulus detection [Parikh *et al.*, 2007]. We hypothesize that ACh release may facilitate task-irrelevant perceptual learning when the task-irrelevant stimuli appear in temporal and spatial proximity to the allocation of spatial attention. Further research will be needed to determine the role of ACh in task-irrelevant perceptual learning (see [Roelfsema *et al.*, 2010] for a review of perceptual learning, attention, and neuromodulatory signals).

In the present study, subjects overall task performance (across both trained and untrained conditions) was impaired by administration of donepezil, indicating that the presumed increase in selectivity of the neural response by ACh did not translate into an overall improvement in motion direction discrimination. However, the decrease in performance could also be the result of other effects of the drug. Donepezil was administered systemically in our study, and although this drug is relatively selective for the form of cholinesterase expressed in the central nervous system [Kosasa *et al.*, 1999], it may have affected non-specific task-related cognitive functions as well as cholinergic synapses regulating processes such as lens accommodation and pupil dilation [Estermann *et al.*, 2006]. These non-specific effects of the drug would have affected performance in all conditions (including both pre- and post-training measurements) but would have been independent of the specific effect of donepezil on the magnitude and specificity of perceptual learning. Importantly, increased learning in the trained condition under donepezil was observed even when performance was normalized to each subjects pre-training threshold. Thus, overall differences in performance do not account for the beneficial effects of the drug on perceptual learning.

In conclusion, we have shown that the rate, magnitude, and specificity of perceptual learning of a visual motion direction discrimination task are greater when donepezil is administered during the training procedure. These findings demonstrate the possibility of enhancing the beneficial cognitive effects of the cholinergic system, even in a young healthy population, and suggest that the cognitive improvement associated with cholinergic enhancement in Alzheimers disease may stem from an augmented capacity to learn new information. Our finding that donepezil increases the specificity of perceptual learning suggests that ACh may augment plasticity and tuning in populations of neurons that encode task-relevant stim-

ulus features.

Chapter 4

Cholinergic Enhancement Increases the Effects of Voluntary Attention but Does Not Affect Involuntary Attention

4.1 Introduction

Selection of incoming sensory information is required for effective processing, and visual spatial attention is one mechanism for selecting particular regions of space [Posner *et al.*, 1982; Prinzmetal and Landau, 2010]. Two distinct types of visual spatial attention have been identified. On the one hand, attention can be voluntarily allocated to a location that is relevant for performing a task [Posner *et al.*, 1982]. On the other hand, attention can be captured in an involuntary fashion by a salient event at a spatial location, even when that location is not task-relevant [Yantis and Jonides, 1990]. These two forms of attention (voluntary and involuntary, or endogenous and exogenous) have different consequences for the processing of visual stimuli [Prinzmetal *et al.*, 2005; Prinzmetal *et al.*, 2008] and are associated with different neural mechanisms [Kincade *et al.*, 2005; Landau *et al.*, 2007; Esterman *et al.*, 2008]. Additionally, involuntary attention is fast to develop but is transient, dissipating quickly [Posner *et al.*, 1982]. In contrast, voluntary attention takes more time to develop [Posner *et al.*, 1982; Prinzmetal and Landau, 2010] but can be sustained for many seconds [Silver *et al.*, 2007].

We examined the role of the neurotransmitter acetylcholine (ACh) in modulating voluntary and involuntary attention in healthy human subjects. ACh has been found to facilitate cognitive processes such as attention and learning [Sarter *et al.*, 2005]. Cholinergic neurons in the basal forebrain project widely to cerebral cortex, where they release ACh when animals are performing attentionally demanding tasks [Arnold *et al.*, 2002]. Conversely, performance in such tasks is impaired when the basal forebrain nuclei are lesioned [Muir *et al.*, 1994]. Cholinesterase inhibitors such as donepezil and physostigmine increase synaptic levels of ACh

by inhibiting the enzymatic breakdown of ACh in the synaptic cleft, and physostigmine has been reported to improve performance on a voluntary visual attention task [Bentley *et al.*, 2004].

We used an anti-cueing task [Posner *et al.*, 1982; Warner *et al.*, 1990; Sereno and Holzman, 1996] (4.1) to separately measure the effects of voluntary and involuntary attention on behavioral performance. A double-blind placebo-controlled crossover design was employed to assess the effects of donepezil on these two types of attention. We found that cholinergic enhancement increased the benefits in performance due to voluntary attention but had no effect on involuntary attention.

4.2 Methods

4.2.1 Subjects

There were twenty participants (ten females, mean age: 23 ± 3), all of whom had normal or corrected-to-normal vision. Tobacco smokers were excluded.

4.2.2 Procedure

Each subject participated in three sessions. In the first session, subjects practiced 500 trials of the behavioral task. Before each of the subsequent sessions, subjects were administered either placebo or 5 mg donepezil. Drug administration was double-blind, and the order of drug and placebo administration was counterbalanced between subjects. For each of the drug and placebo sessions, subjects performed 1000 trials of the task (approximately 1 hour of testing). Testing started three hours after the pill was administered, corresponding to the time of peak plasma concentration of donepezil following oral ingestion [Rogers *et al.*, 1998]. At least two weeks passed between the second session and the third session, allowing the drug, if present, to be eliminated. While performing the task, participants were seated in a dark room, with their eyes 50 cm from the display and their chin placed in a chin rest. They were instructed to fixate on a central point, and eye movements were monitored with an infrared camera. Subjects received auditory feedback at the end of a trial if they failed to maintain fixation. Donepezil has previously been found to have no effect on fixation stability at the 5 mg dose used in the present study [Silver *et al.*, 2008]. The proportion of trials in which eye movements occurred was generally low (0.5% of all trials) and did not differ between drug and placebo sessions ($F_{1,18} = 0.1$, $p = 0.8$)

4.2.3 Task

An anti-cueing task was used to dissociate voluntary and involuntary attention [Posner *et al.*, 1982; Warner *et al.*, 1990; Sereno and Holzman, 1996] (Figure 4.1). Each trial began

with a 200 msec cue: one of the peripheral rectangular frames became black and slightly thicker (from 0.1 to 0.24 degrees of visual angle). The appearance of this cue in one location predicted the appearance of a target grating in the opposite location for 80% of the trials and in the same location as the cue for the remaining 20% of trials. The target display contained twelve Gabor patches (100% contrast, spatial frequency of 2 cycles/degree; space constant of 0.8 degrees), three within each frame. The target (always the central of the three Gabor patches) was tilted ±45 degrees away from vertical, and all other patches were vertically oriented. Subjects were instructed to report the direction of tilt of the target by pressing a button as accurately and as quickly as they could. Auditory feedback on performance was provided at the end of each trial. In different blocks (250 trials per block), the stimulus onset asynchrony (SOA) between the appearance of the cue and the appearance of the target was either 40 or 600 msec. The target display appeared for 133 msec in 40 msec SOA blocks and for 333 msec in 600 msec SOA blocks. Visual stimuli were presented on a CRT monitor, using the Psychophysics Toolbox [Brainard, 1997; Pelli, 1997].

4.2.4 Analysis

Trials in which eye movements occurred were excluded from analysis. In addition, trials with RTs faster than 100 msec or slower than 1000 msec were excluded from the analysis, as were trials with RTs more than three standard deviations away from the mean for that condition. Mean RTs were analyzed in a mixed model ANOVA. Cue (target in the cue or opposite location), drug (placebo or donepezil) and SOA (40 or 600 msec) were entered as within-subject factors, and order (placebo first or donepezil first) was entered as a between-subject factor.

4.3 Results

An anti-cueing task [Posner *et al.*, 1982; Warner *et al.*, 1990; Sereno and Holzman, 1996] was used to measure the effects of voluntary and involuntary attention. Each trial began with a cue in one of four locations, predicting the subsequent appearance of the target in the opposite location for 80% of the trials (Figure 4.1). In the remaining 20% of trials, the target appeared in the same location as the cue. For all trials, involuntary attention is initially drawn to the appearance of the salient cue. With increasing time following cue presentation, voluntary attention can be allocated to the opposite location (where the target was presented for 80% of the trials). In order to separately examine the effects of involuntary and voluntary attention, the stimulus onset asynchrony (SOA) between the cue and target was varied between blocks.

We first describe the effects of spatial cueing following placebo administration. For half of the blocks, the SOA was 40 msec, corresponding to an interval for which involuntary

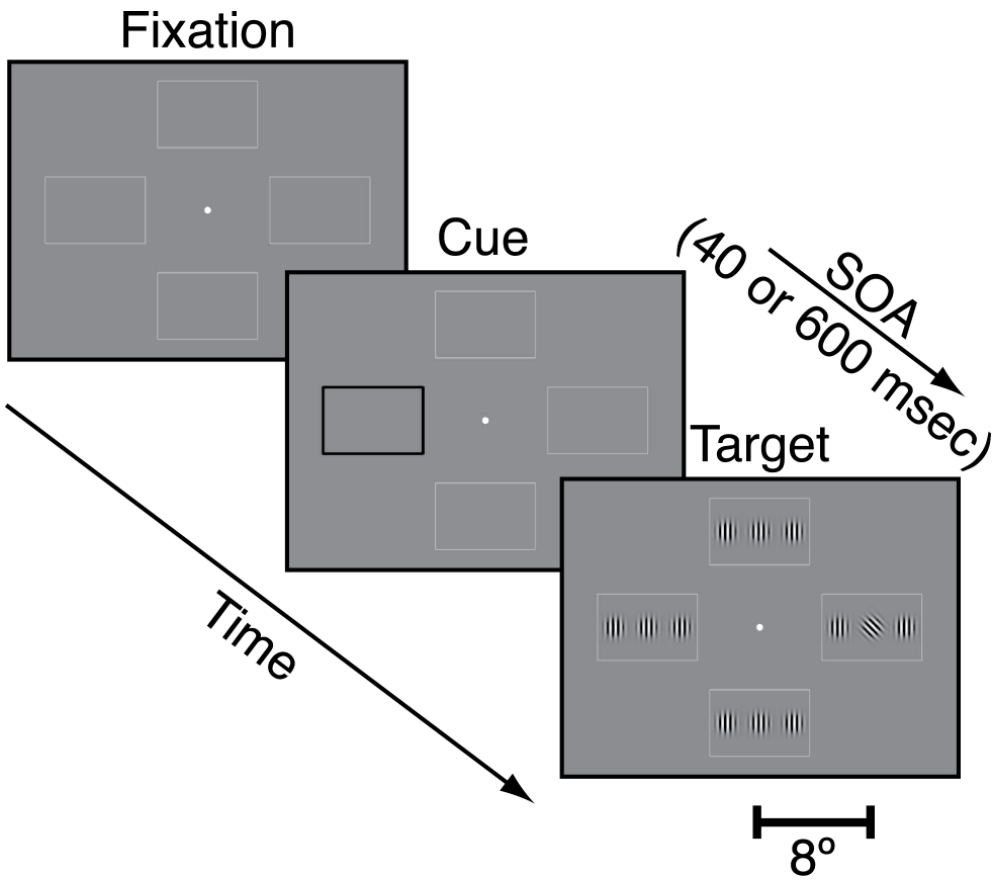

Figure 4.1: *Anti-cueing task*. At the beginning of each trial, one of the four peripheral rectangular frames became black and thicker. This cue indicated that the target would be most likely (80%) to appear in the opposite location following an SOA of either 40 or 600 msec. In the remaining 20% of trials, the target appeared at the cue location. The target was a Gabor patch oriented ± 45 degrees relative to vertical. Subjects indicated target orientation as quickly and accurately as they could by pressing one of two buttons.

attention is still present in most subjects, but voluntary attention has not yet been allocated [Posner *et al.*, 1982]. In these blocks, reaction times (RTs) to target presentation were faster in the cue location (518 msec) compared to the opposite location (538 msec) (Figure 4.2 2). The mean cueing effect (the difference between cue location and opposite location RTs) for short SOA trials was -20 msec. This measure was negative in 17 of 20 subjects, suggesting that involuntary attention was successfully captured in the 40 msec SOA condition in most of the participants.

In the remaining blocks, the SOA was 600 msec. This allowed sufficient time for involuntary attention in the cue location to dissipate and for allocation of voluntary attention to the opposite location, where the target was likely to appear (80% probability). In these blocks, the mean RT was faster when the target appeared in the opposite location (491 msec) compared to the cue location (522 msec) (Figure 4.2). The cueing effect for these long SOA trials was positive in all subjects, as was the average cueing effect (32 msec). Moreover, the interaction of SOA and cue was significant ($F_{1,18} = 75.4$, $p < 0.01$), indicating that short and long SOAs produced different patterns of RTs. Indeed, the difference between the cueing effect in the long and short SOA conditions was positive in all 20 subjects (mean = 52 msec). These results (in the placebo condition) replicate previous findings obtained using the anti-cueing procedure [Posner *et al.*, 1982; Warner *et al.*, 1990; Sereno and Holzman, 1996].

In order to test the effects of acetylcholine on voluntary and involuntary attention, the cholinesterase inhibitor donepezil was administered. Each subject received 5 mg donepezil before one session and placebo before the other session. There was no effect of drug administration on overall mean RT (placebo = 517 msec; donepezil = 514 msec; $F_{1,18} = 0.3$, $n.s.$). In fact, donepezil had an effect in only one of the four conditions: SOA of 600 msec and target in the opposite location (placebo = 491 msec; donepezil = 483 msec; Figure 4.2), and this difference was significant in a planned comparison ($t_{18} = 3.3$, $p < 0.05$). No effect of the drug was found in planned comparisons for the other three conditions. Furthermore, the interaction of drug administration, cue and SOA was also significant ($F_{1,18} = 4.4$, $p < 0.05$). Additionally, in the long SOA condition, the cueing effect was larger for donepezil than for placebo (Figure 4.3 planned comparison, $t_{18} = 2.6$, $p < 0.05$), providing further evidence that cholinergic enhancement augmented voluntary but not involuntary attention. Taken together, the RT and cueing effect results demonstrate that cholinergic enhancement increased the effects of voluntary attention on performance. In particular, there was a selective advantage when voluntary attention enhanced processing of the stimulus namely, when there was sufficient time for voluntary attention to be deployed and when the target was presented in the opposite (attended) location.

The lack of a main effect of the drug on RT or on any other combinations of SOA and target location rules out the possibility that the drug had a nonspecific overall effect on performance. Moreover, the high degree of similarity in task demands and stimulus characteristics across SOAs and target locations suggests that the drug effects measured at

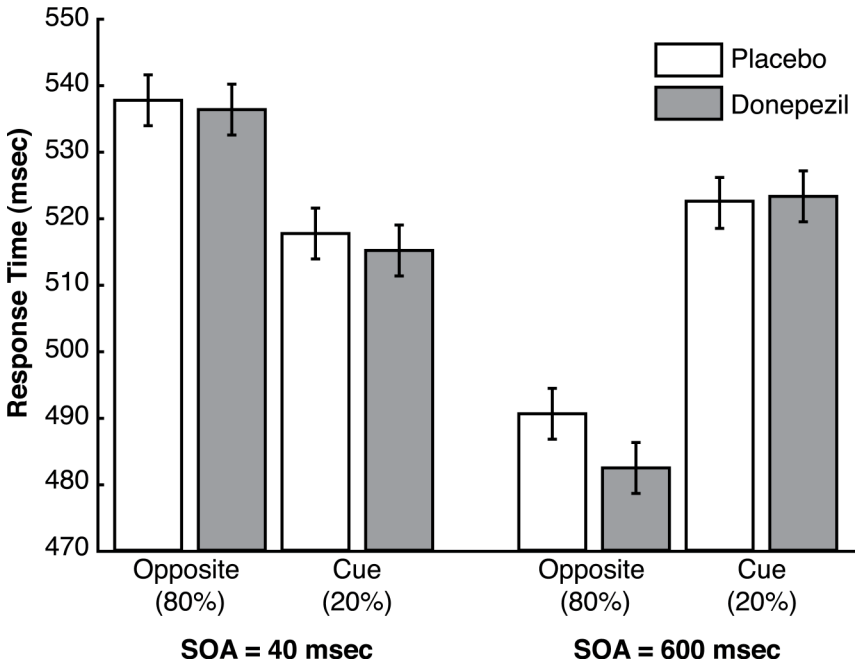

Figure 4.2: *Effects of cue location, SOA, and drug condition on reaction times.* Reaction times in placebo (white) and donepezil (gray) sessions. For trials in which the SOA was 40 msec (left), RTs were significantly faster for the 20% of trials in which the target appeared in the same location as the cue, indicating capture of involuntary attention. For trials in which the SOA was 600 msec (right), RTs were significantly faster for the 80% of trials in which the target appeared in the opposite location, indicating allocation of voluntary attention. Donepezil reduced RTs in only one of the four conditions: 600 msec SOA trials in which the target appeared in the location opposite to the cue. Error bars are within-subject errors, calculated from the error term in the highest-order interaction in the analysis of variance [Loftus and Masson, 1994]

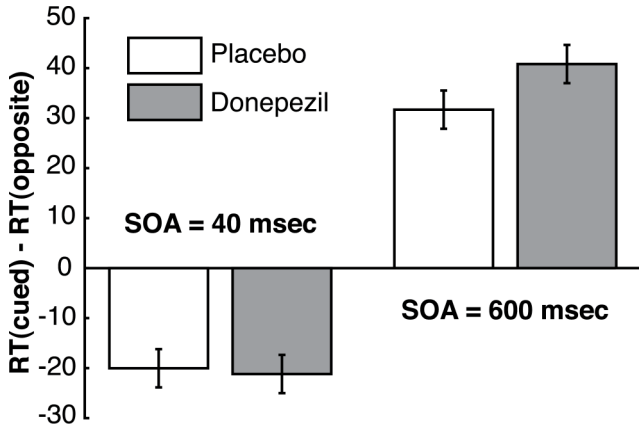

Figure 4.3: *Cholinergic enhancement increases cueing effects for voluntary but not involuntary attention*. The cueing effect is defined as the difference between the mean RT for trials in which the target appeared at the cue location and the mean RT for trials in which the target appeared at the opposite location. Cueing effects for placebo (white) and donepezil (gray) are presented. For 40 msec SOA (left), the cueing effect was negative, indicating capture of involuntary attention at the cue location. For 600 msec SOA (right), the cueing effect was positive, indicating that voluntary attention was allocated to the location opposite the cue location. Cholinergic enhancement increased the magnitude of the cueing effect only for the 600 msec SOA trials. Error bars are as in Figure 4.2.

long SOAs reflect a specific enhancement of voluntary allocation of attention (rather than interactions between drug and stimulus properties).

A significant interaction of session order and drug ($F_{1,18} = 33.3$, $p < 0.01$) indicates that there was an overall effect of practice on performance. In particular, RTs were faster in the second session (501 msec) than in the first session (531 msec). There were no higher-order interactions of the order of drug administration with any of the other factors in the analysis of variance, indicating that the practice effect (the improvement in RTs in the second session) was not specific to any single attention condition.

Subjects were instructed to respond as quickly and as accurately as they could. Performance was well above 90% correct in all conditions (mean: 94.5%), and the analysis of RT was restricted to trials in which a correct response was made. Nevertheless, we measured the effects of voluntary and involuntary attention and cholinergic enhancement on behavioral accuracy. Like the RT findings, there was a significant interaction of cue and SOA on percent correct ($F_{1,18} = 27.4$, $p < 0.01$). This effect was modest in magnitude, resulting in a cueing effect of 1.7% correct in the long SOA blocks (greater accuracy for opposite location compared to cue location trials). In the short SOA blocks, the cueing effect on accuracy was -1.8% correct, indicating a decrease in performance for targets at the opposite location relative to cue location, due to capture of involuntary attention by the cue. Importantly, administration of the drug had no overall effect on accuracy ($F_{1,18} = 1.3$, $p = 0.3$), and there was no significant interaction of drug administration with either cue or SOA in the analysis of performance accuracy.

4.4 Discussion

We found that pharmacological enhancement of the cholinergic system in healthy human subjects increases the effects of voluntary but not involuntary attention. These results provide further evidence that voluntary and involuntary attention have different neural substrates [Kincade *et al.*, 2005; Landau *et al.*, 2007; Esterman *et al.*, 2008]. Allocation of voluntary attention can improve processing at an attended location at the cost of impaired processing in other locations [Bashinski and Bacharach, 1980; Posner *et al.*, 1980]. Our results suggest that cholinergic enhancement specifically increases benefits of voluntary attention for processing stimuli at the attended location. Another possible explanation of our findings is that donepezil causes a shift in baseline performance, accompanied by a change in both the costs and the benefits due to voluntary attention. Because we did not include a neutral condition in which the cue provided no information about subsequent target location, we cannot determine whether there is a pharmacological effect on baseline performance. However, we found no effect of donepezil on overall RT (across all conditions). In addition, donepezil reduced RTs only when targets appeared at the location at which voluntary attention was directed. We therefore favor the more parsimonious explanation: cholinergic enhancement

causes a specific increase in the processing benefits due to voluntary attention.

A number of studies have assessed the effects of the ACh receptor agonist nicotine in spatial cueing tasks. Some have found a reduction in the size of the validity effect (RT difference between valid and invalid trials) in humans [Meinke *et al.*, 2006; Vossel *et al.*, 2008], while others have not [Giessing *et al.*, 2006; Griesar *et al.*, 2002]. Consistent with our results, Meinke et al. (2006) reported an effect of nicotine on voluntary but not involuntary attention. However, unlike our finding that donepezil selectively increased the benefits of voluntary attention, nicotine decreased the benefits (valid trials) as well as the costs (invalid trials) of voluntary attention [Meinke *et al.*, 2006]. Moreover, nicotine reduced overall RT [Griesar *et al.*, 2002; Meinke *et al.*, 2006], suggesting a possible non-specific effect of this drug, while there was no main effect of donepezil on RT in the present study. It is difficult to directly compare the results of the two studies, because in the Meinke et al. (2006) study, voluntary and involuntary attention trials differed in the type of cue (central versus peripheral), SOA, and the proportion of valid and invalid trials. In contrast, our design utilized identical cues, targets, and cue validity, with involuntary and voluntary attention trials differing only in SOA and target duration.

In addition, nicotine is an agonist of only the nicotinic subtype of ACh receptors, and physiological evidence suggests that the effects of voluntary visual spatial attention on activity of neurons in primary visual cortex are mediated by muscarinic ACh receptors [Herrero *et al.*, 2008]. Receptor agonists and antagonists interact directly with subtypes of ACh receptors at all synapses where those receptor subtypes are located, independent of the amount of endogenous activity at those synapses. In contrast, cholinesterase inhibitors preferentially enhance cholinergic transmission at those synapses that are endogenously releasing ACh during performance of a given task. They are therefore more physiologically relevant than receptor agonists and antagonists for the study of the role of the cholinergic system in modulation of behavior and neural processing.

Cholinesterase inhibitors such as donepezil and physostigmine increase synaptic levels of ACh by inhibiting the enzymatic breakdown of ACh in the synaptic cleft and are frequently used in humans to mitigate cognitive decline in Alzheimer's disease. Some studies have found that cholinesterase inhibitors significantly affect measures of cognitive function and quality of life in patients with Alzheimer's disease [Mohs *et al.*, 2001; Boada-Rovira *et al.*, 2004], but the utility of their administration is still controversial [Courtney *et al.*, 2004; Raschetti *et al.*, 2007]. Therefore, it would be beneficial to have a more complete understanding of the specific aspects of cognition and behavioral performance that are pharmacologically enhanced by increases in synaptic ACh.

Physostigmine administration has been reported to improve performance on a voluntary visual attention task [Bentley *et al.*, 2004], but reduced RTs were observed in this attention task as well as other visual tasks. This generalized improvement suggests that physostigmine may have produced an increase in vigilance and/or arousal that was not specific to visual spatial attention. In the present study, no such generalized effect was found, suggesting that

the results are due to effects of the drug on attention and not on vigilance and/or arousal.

The increase in the benefits conferred by voluntary attention could be a result of at least two possible physiological mechanisms. The first mechanism is a direct 'bottom-up' modulation of visual processing of the target stimulus in early visual cortical areas. Animal studies have shown that ACh increases thalamocortical synaptic transmission relative to lateral intracortical connections [Giocomo and Hasselmo, 2007]. ACh reduces the lateral spread of excitatory activity in rat visual cortical slices [Kimura *et al.*, 1999] and decreases the optimal stimulus length for cells in marmoset area V1 [Roberts *et al.*, 2005]. In humans, administration of donepezil decreases the spatial spread of excitatory fMRI visual responses in early visual cortex, consistent with a reduction in excitatory receptive field size in visual cortical neurons [Silver *et al.*, 2008]. Thus, increasing ACh levels may result in a more reliable representation of the stimulus in visual cortex. We hypothesize that voluntary attention may cause spatially and/or temporally specific increases in ACh levels in cortical regions that contain neurons representing the attended visual field location. The resulting boost in thalamocortical transmission may act to gate sensory signals in these neurons, thereby facilitating processing of stimuli at the attended location. This hypothesis is consistent with a recent study that found that ACh can be released in cortex in a transient and spatially specific manner [Parikh *et al.*, 2007].

A second possible physiological mechanism ('top-down') is an increased effect of ACh in attention control areas in frontal and/or parietal cortex. Local increases in ACh concentrations in prefrontal cortex correlate with behavioral performance in a task requiring attention [Parikh *et al.*, 2007]. Increased cholinergic neurotransmission in frontal cortex may potentiate activity in frontal and parietal cortical areas that have been associated with control of voluntary attention [Serences and Yantis, 2006] and may consequently improve performance in the voluntary attention condition. Further research is needed to distinguish these two possible mechanisms of cholinergic modulation of voluntary attention.

In conclusion, we have demonstrated that cholinergic enhancement with donepezil selectively augments voluntary attention with no measurable effects on involuntary attention. These findings suggest that voluntary and involuntary attention are associated with different neural mechanisms. Finally, these results shed light on the role of the cholinergic system in modulation of cognitive functions in humans and demonstrate the potential to enhance these functions through pharmacological manipulations.

Chapter 5

Summary and conclusions

In this part of the thesis I will summarize and draw some general conclusions from the studies presented in Chapters 2, 3 and 4. In particular, I will try to address the connection between the different studies presented in each of these Chapters and I will try to explain how the results of these studies may help to address questions and hypotheses raised in the introduction. After summarizing the main findings, I will address the role of attention in learning. I will review some of the previous findings concerning the role of attention in learning and how the our pharmacological results may provide novel interpretations of these previous findings. Then, I will turn to implications of the findings presented here to the question of changes in representation in perceptual learning. I will present some ideas for future studies designed to address these implications and to refine our conclusions.

Though we have not tested a clinical population in any of the studies described here, donepezil is currently under clinical use for the treatment of Alzheimer's disease (AD). Therefore, I find it appropriate to briefly review the clinical literature on the cognitive benefits of donepezil administration in AD and to ask whether we have learned anything from the findings presented here about these clinical benefits. I will also hypothesize about the potential use of donepezil, in conjunction with perceptual learning, in the treatment of other clinical conditions and in particular in the treatment of amblyopia.

5.1 Cholinergic enhancement augments perceptual learning

Acetylcholine (ACh) has previously been found to play a role in learning and attention in many experiments, mostly in animal models (see review in Chapter 1 and in the introductions to Chapters 3 and 4).

Therefore, the main experimental hypothesis we have pursued here is that perceptual learning would be augmented in healthy human subjects by pharmacologically enhancing the

cholinergic system in these subjects. This hypothesis is confirmed by the results presented in Chapter 3. Perceptual learning of a motion direction discrimination task was found to be more pronounced under cholinergic enhancement and more specific to the trained condition.

Chapter 2 provides a theoretical framework within which this result can be interpreted, while Chapter 4 provides further evidence for the role of ACh in the allocation of visual spatial attention. Taken together, the results presented in Chapter 3 and in Chapter 4 suggest a role for voluntary visual spatial attention in perceptual learning of the task.

5.2 The role of attention in learning

Previous work has addressed the question of the role of attention in learning by requiring subjects to allocate attention to particular features of the training stimulus [Ahissar and Hochstein, 1993] Other studies have drawn attention away from the spatial location of the learned stimuli, by requiring the subjects to perform a demanding task at the center of the visual field, while a subthreshold stimulus was presented in peripheral vision [Watanabe *et al.*, 2001]. Initially, it seemed that these two studies lead to disparate conclusions. On the one hand, learning seems to be rather specific to a feature on which a discrimination is performed during training, generalizing only very poorly to other features of the same stimulus [Ahissar and Hochstein, 1993]. On the other hand, rather robust and specific perceptual learning can occur for stimuli from which attention is actively withdrawn. These stimuli could not be detected, even if attention had not been withdrawn away from them, because the stimulus was presented at a sub-threshold level. More recently, additional data suggests that these two findings may reflect similar mechanisms. First, learning without attending to the training stimulus seems to be both temporally [Seitz and Watanabe, 2003] and spatially [Nishina *et al.*, 2007] specific. In addition, learning does not occur when the stimulus to be ignored is presented at a supra-threshold intensity [Tsushima *et al.*, 2008]. This has led to the hypothesis that supra-threshold stimuli and features are subject to attentional suppression when subjects are actively ignoring them, but when the same stimulus is presented at a sub-threshold intensity, it may result in perceptual learning, because it is not actively inhibited [Roelfsema *et al.*, 2010].

The pharmacological study in Chapter 3 addresses the role of attention in learning indirectly, not by manipulating the amount of attention that the subjects are asked to allocate to the learned stimulus, but presumably by pharmacologically altering the amount of attention that subjects *can* allocate to the stimulus. The results of the attention experiment in chapter 4 provide supporting evidence to this conjecture. Moreover, these results suggest that perceptual learning is mediated by *voluntary* attention, rather than involuntary attention, which was unaffected by the pharmacological manipulation.

Voluntary attention could therefore be the solution to the problem described in 1.3 [Hasselmo, 1993]. When voluntary attention is directed to a stimulus (and ACh is released in

sensory cortex) this provides the neurons in cortex with more feedforward information from the sensory organs and this pattern of activity also drives plasticity in cortex. However, the research presented here provides only indirect evidence for this conclusion and further research is needed in order to test it more thoroughly.

5.3 Change in representation?

A series of recent behavioral studies of perceptual learning suggests that the extent [Kuai *et al.*, 2005; Zhang *et al.*, 2008] and specificity [Zhang *et al.*, 2009; Xiao *et al.*, 2008] of perceptual learning may depend on the pattern of stimulus presentation. In particular, when the stimuli unpredictably vary along some parameter from trial to trial (roving stimuli), learning does not occur [Kuai *et al.*, 2005]. However, if subjects are provided with enough information to predict which stimulus is about to be presented in each trial, learning does occur [Zhang *et al.*, 2008]. Conversely, when subjects are provided with information about additional peripheral locations in which testing may occur, either by conducting a pre-testing procedure in an additional location [Zhang *et al.*, 2009] or by conducting training on another task in an additional location [Xiao *et al.*, 2008] learning can generalize beyond the trained location. These results strongly suggest that the extent and specificity of learning can be modulated according to the expectations of the subject during learning. These results may be interpreted as evidence that learning can be flexibly adjusted to occur at the level of the visual system at which the most benefit would be provided, given the particular statistics of the input (as suggested in [Ahissar and Hochstein, 1997; Ahissar and Hochstein, 2004]). Alternatively, these results may reflect learning always occurring at a higher level of processing or decision-making, which is not specific to a particular stimulus condition. Under this model (e.g. [Yu *et al.*, in review]) generalization to other stimulus conditions will occur if connections between higher levels and lower levels are established during training, without a requirement for extensive training to occur in these other conditions.

The theoretical model presented in Chapter 2 suggests that the oblique effect is a consequence of the unequal representation of oblique and cardinal orientations and directions in early stages of cortical visual processing. Thus, this model predicts that perceptual learning of motion direction discrimination may be a consequence of encoding of motion direction by populations of neurons in areas such as V1 and MT. However, a further consequence of this model is that it may not be enough to only change the representation in primary visual cortex but that changes must also occur in the way in which the information is decoded in subsequent stages of processing. A recent study [Law and Gold, 2008] has found substantial changes occurring in the responses of cells in macaque area LIP when the monkeys were trained on a perceptual task. In order to address this hypothesis, in a continuation of the studies presented here, we are using fMRI and an analysis of the functional connectivity between early cortical visual areas, such as V1 and MT+ and areas in parietal cortex, which

may comprise a human analogue of macaque area LIP (but see [Patel *et al.*, 2010], for a recent study which suggests that there may be some differences between the species). These areas contain ordered representations of the allocation of visual spatial attention to different regions in the visual field [Silver *et al.*, 2005]. In a previous study in the lab [Lauritzen *et al.*, 2009], fMRI coherency analysis [Sun *et al.*, 2004] was used in order to measure changes in connectivity between these parietal regions and visual areas in occipital cortex when subjects allocate visual spatial attention. In our future studies, this analysis technique will be used in order to measure the changes in functional connectivity between parietal regions and areas containing neurons that are selective for motion direction and may provide the necessary information for performance of the direction discrimination task.

Future theoretical work will expand the population-coding model presented in Chapter 2, focusing on changes in the network of connections between visual areas with learning and the role of attention and ACh in these changes. These simulations will be informed by the results of the ongoing fMRI experiments.

5.4 Donepezil and Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia. AD is characterized by a selective degeneration of cholinergic neurons in the basal forebrain [Whitehouse *et al.*, 1982]. Therefore, the most common treatments for AD is the administration of cholinesterase inhibitors (ChEI). Donepezil is considered a "second generation" ChEI and, due mostly to its low prevalence of side effects relative to other ChEIs such as galantamine and rivastigmine, it is the most widely prescribed pharmacological treatment for AD [Pariente *et al.*, 2008; Mucha *et al.*, 2008]. Presumably, donepezil and the other ChEIs exert their clinical effects by inhibiting hydrolysis of ACh by the enzyme acetylcholinesterase, thus raising the levels of ACh in CNS synapses when ACh is endogenously released.

The clinical benefits due to administration of donepezil have been estimated in several clinical studies. Different studies reviewed by Birks and Harvey [Birks and Harvey, 2006] have measured benefits in the cognitive domain, using standard questionnaires for assessing daily life activities, quality of life, deterioration due to the the disease, neuropsychiatric symptoms and health resource utilization, as well as stress in care-givers. Their review of the literature concluded that, relative to placebo, donepezil administration results in benefits in the cognitive domain. In addition, the administration of donepezil led to a benefit in measures of daily life activities and global clinical state and of clinician-rated measures of dementia.

However, the delay in institutionalization in patients may have been rather small and no benefit was found in health resource utilization. One of the studies reviewed [Courtney *et al.*, 2004] endeavoured to measure the effects of donepezil on the cost of treatment in a sample of patients which were not enrolled using the rigorous exclusion criteria usually used

in drug-company-sponsored clinical trials (which may bias the results of these trials). In addition, this study measured the clinical benefits of donepezil for an unusually long period of up to 4 years. This study raised the possibility that the cognitive benefits of treatment with donepezil do not extend to benefits in cost of care and in addition raised the possibility that the cognitive benefits may be limited to the first year of treatment. However, this study suffered from an unusual number of methodological difficulties, such as patient attrition, thereby limiting the conclusions that could be drawn from it.

Though we have studied a healthy population of young subjects, our studies suggest that some of the cognitive benefit of donepezil for the clinical population may stem from an improvement in the allocation of attention and a subsequent improvement in the ability to learn and retain information. However, given the vast differences between the population we have studied and the clinical population as well as the potential differences between perceptual learning and other forms of learning, this remains an extrapolation from the data, rather than a straight-forward conclusion and further research on a clinical population would be needed in order to conclusively determine whether this is the case.

5.4.1 Other potential clinical uses of donepezil and perceptual learning

Perceptual learning has been suggested as a tool not only for studying the brain, but also for treating clinical conditions, such as dyslexia [Temple *et al.*, 2003] and amblyopia [Levi and Polat, 1996; Polat *et al.*, 2004]. In several studies in patients with amblyopia (reviewed in [Levi and Li, 2009]), perceptual training on a variety of different tasks and stimuli seems to transfer to general benefits in visual acuity. In many of these studies, many hours of training were administered and it would seem like the addition of a pharmacological treatment which would speed up learning could be beneficial. However, though differences in the duration of training between different studies predict the differences in the magnitude of learning of the trained task, these differences in duration do not predict the magnitude of improvement in the general benefits on visual acuity. Therefore, it is not clear that there would be any benefit in administering donepezil to patients undergoing perceptual learning as a clinical treatment. The increased specificity of learning might also pose a problem in this context, as typically, the goal of perceptual learning in clinical applications is to generalize beyond the trained condition and this generalization is decreased (specificity is increased) in the study presented in Chapter 3.

5.5 Conclusions

The goal of this dissertation has been to understand the mechanisms underlying perceptual learning in the human visual system. Chapter 3 constitutes the main result: the amount and specificity of perceptual learning is augmented in healthy human subjects when the

cholinergic system is pharmacologically enhanced. Chapter 4 provides converging evidence with regard to the role of ACh in attention and in particular in voluntary attention and the role that attention may play in perceptual learning. Chapter 2 provides a theoretical framework with which to understand these results and serves as the basis for interpreting and modeling future results.

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