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Cholinergic Modulation of Visual Perceptual Learning of Texture Discrimination



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# Cholinergic Modulation of Visual Perceptual Learning of Texture Discrimination

By

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University of California, Berkeley

Committee in charge:

Professor Michael A. Silver, Chair
Professor Dennis M. Levi
Professor Mark D'Esposito

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Abstract

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Acetylcholine is a neuromodulator implicated in cognitive processes such as attention and memory, as well as the regulation of sensory cortical plasticity. In animal models, acetylcholine boosts the amplitude of visually evoked cortical responses, especially to behaviorally pertinent stimuli. Perceptual learning is a well-studied manifestation of sensory cortical plasticity, and can be induced and subtly probed in humans with minimal invasiveness. Previous studies of the effects of pharmacological cholinergic enhancement on perceptual learning in humans have yielded mixed results across different tasks. In this dissertation, I present two experiments that combine behavioral pharmacology and repeated psychophysical training in healthy human subjects to assess the effects of increased cholinergic neurotransmission on a broadly used and thoroughly studied measure of visual perceptual learning: the texture discrimination task.

In Chapter 2, I describe a study of the effects of transient cholinergic enhancement (a single drug dose administered at training's onset) on perceptual learning induced by a brief course of texture discrimination task training. The results indicate that transient cholinergic enhancement neither increased nor decreased the extent or location selectivity of texture discrimination learning, and are consistent with several competing interpretations. One possibility is that the plasticity mechanisms mediating improved texture discrimination performance are impervious to cholinergic modulation. Conversely, it is also possible that cholinergic effects on texture discrimination learning would have emerged had our drug administration and/or training procedures been more substantial and/or prolonged.

I address this second possibility directly in the experiment detailed in Chapter 3. This study assesses the effects of sustained cholinergic enhancement (multiple drug doses administered throughout training) on perceptual learning during a course of texture discrimination training over several days. The results demonstrate that sustained cholinergic enhancement significantly increased the magnitude, but neither the location nor background orientation specificity, of texture discrimination learning compared to placebo. These results shed light on

the interpretation of the findings discussed in Chapter 2, and demonstrate that the processes underlying improved performance on the texture discrimination task are indeed susceptible to cholinergic modulation. While sustained cholinergic enhancement significantly boosted texture discrimination learning's magnitude, it also tended to reduce the background orientation specificity of this learning. This suggests that selective facilitation of plasticity for the neuronal population representing task-relevant stimuli is unlikely to be the primary biological mechanism through which cholinergic enhancement bolsters texture discrimination learning. Other possibilities consistent with the results include cholinergic effects on visual responsiveness, attention, and memory consolidation.

Dedicated with love to the memory of my father,
Robert Edward Byrne,
inspirer of fierce curiosity and big dreams.

*Wish you were here to see this.*

## Acknowledgments

Reflecting on the trail I've hiked to my doctorate, I feel tremendously fortunate to have been so well supported and cared for along the way. My search for words that properly convey the gratitude I feel is ongoing, but it is time to put some to paper.

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There's a proverb that holds, "Joy shared is doubled; sorrow shared is halved." I am supremely thankful to those who have been my closest confidants during graduate school for exemplifying the truth in this maxim. Ally Boehm quickly became my first friend in the United States of California and has made a new place feel like home. Cécile Fortuny and Jes Wei made preparing for quals bearable in the moment but enjoyable in retrospect, and engineered many revitalizing travels and adventures. Cécile, particularly during the past chaotic year, has bolstered me against every obstacle and doubt that threatened to deter my course – crossing this finish line together makes the victory taste sweeter. I would never have applied to Berkeley were it not for Zach Helft, who helped and encouraged me then and has never stopped. Zach has been a constant guide and companion on this trail, and had my back every step of the way. You said it best, Zach: I can think of no better friend.

Finally, the most emphatic and enthusiastic thanks go to my loving family for cheering me on loudly and proudly throughout this and every period of my life. Sol, my eternal puppy, thank you for bringing me unmatched joy. To my siblings Erin and Tim, thank you for continually inspiring me to do and be better in every way, and for making me exceptionally proud. I am thankful most of all to my parents, who set me on this path by raising me to value truth, knowledge, accountability, perseverance, and integrity. To my first, best teacher and eternal role model, my mother, Carolyn - thank you for a lifetime of unconditional love and support. I am more grateful to be your daughter than just about anything else.

## TABLE OF CONTENTS

## 1 | Introduction

Behavioral improvements stemming from repeated sensory experience or sensory task practice are a type of nondeclarative learning called perceptual learning (PL). PL is a ubiquitous phenomenon that occurs in human audition (Kraus et al., 1995), gustation (Peron & Allen, 1988), olfaction (Bende & Nordin, 1997), somatosensation (Pleger et al., 2003), and vision (Poggio, Fahle, & Edelman, 1992). Visual PL occurs across a broad range of behavioral tasks both in the laboratory (Fine & Jacobs, 2002) and everyday life (Shen, Mack, & Palmeri, 2014). Perceptual performance gains are often enduring and specific to the exposure parameters, suggesting their emergence from long-lasting and precise experience-dependent neural modifications. While pioneering physiology work suggests that some forms of experience-dependent plasticity in visual cortical neurons are largely restricted to a critical period early in life (Hubel & Wiesel, 1970), visual PL occurs readily into adulthood and old age (Andersen et al., 2010; McKendrick & Battista, 2013).

Because it presents a non-invasive method for probing plasticity in developed cortex, affords therapeutic promise (Astle, Webb, & McGraw, 2011), and has the potential to improve applied training processes (Deveau & Seitz, 2014), visual PL is of great interest to scientific researchers and clinicians. While our basic understanding of the generation and maintenance of visual PL has advanced greatly over the past five decades (Sagi, 2011; Li, 2016) many fundamental questions, particularly about rules governing the underlying neural plasticity (Sasaki, Náñez, & Watanabe, 2010; Watanabe & Sasaki, 2015), remain. One broad question, reviewed in Roelfsema, van Ooyen, & Watanabe (2010), is: how do neuromodulators shape PL? This dissertation addresses how one neuromodulator, acetylcholine (ACh), influences the magnitude and specificity of visual PL for one task: the texture discrimination task.

Since its introduction to the literature by Karni & Sagi (1991), the texture discrimination task (TDT) has been re-employed extensively and is one of the best-described visual PL tasks. Texture discrimination learning is specific to the trained location, background element orientation, and eye when training is monocular (Karni & Sagi, 1991), consistent with functional change in V1 where both retinotopic and monocular representations exist. Human neuroimaging evidence also supports a contribution of early visual cortical plasticity toward TDT learning (Schwartz, Maquet, & Frith, 2002; Yotsumoto et al., 2008, 2009; Ahmadi et al., 2018). The consolidation and preservation of TDT learning benefit from rapid eye movement (REM) sleep following training (Karni et al., 1994; Stickgold et al., 2000; Mednick, Nakayama, & Stickgold, 2003; McDevitt, Duggan, & Mednick, 2015). Interestingly, ACh release during REM sleep is greater than during other sleep stages and wakefulness (Jasper & Tessier, 1971; Marrosu et al., 1995).

Only one previous study has investigated cholinergic modulation of TDT learning. Beer and colleagues (2013) found enhanced texture discrimination learning in a group of observers that chewed tobacco (containing nicotine, a

cholinergic receptor agonist) after TDT training compared to a placebo-chew group. The specificity of texture discrimination learning to the trained location and background orientation however, was not significantly affected by nicotinic receptor activation. These results demonstrate that TDT learning can be increased by exogenous nicotine administration. It is difficult, however, to draw any inferences about what role endogenous cortical cholinergic transmission might play in the expression of PL from these findings. This is because nicotine, once introduced into cortex, will bind any affinitive receptor it contacts, qualitatively altering the landscape of cholinergic transmission. Alternatively, cholinesterase inhibitors like the Alzheimer's medication donepezil quantitatively boost endogenous cholinergic transmission without changing its qualitative nature by slowing ACh metabolism.

Here, I present two studies designed to explore the effects of enhancing endogenous cortical cholinergic signaling on perceptual learning of the TDT. In the first study, described in Chapter 2, I explored the impact of pairing transient cholinergic enhancement (a single donepezil dose) with a brief course of behavioral training on the magnitude and selectivity of texture discrimination learning. The results showed no discernable effects of transient endogenous cholinergic enhancement with donepezil on either the extent or specificity of TDT learning. In the second study, detailed in Chapter 3, I reutilized the double-blind placebo-controlled design employed in the first to assess the effects of combining sustained cholinergic enhancement (multiple daily donepezil doses) with a prolonged training schedule on the magnitude and selectivity of texture discrimination learning. Sustained cholinergic enhancement with donepezil significantly increased the magnitude, but not the specificity, of TDT learning. Overall, these results support the hypothesis that endogenous cortical cholinergic signaling facilitates texture discrimination learning.

## 2 | Transient cholinergic enhancement does not facilitate perceptual learning of visual texture discrimination

### 2.1 | Introduction

Perceptual learning (PL) is a type of nondeclarative learning in which training improves performance on a sensory task. The benefits of PL are long lasting and are often specific to the stimuli employed during training. PL has been used therapeutically to treat perceptual impairments associated with amblyopia (Levi & Polat, 1996; Polat et al., 2004; Levi & Li, 2009; Chung, Li, & Levi, 2012), myopia (Durrie & McMinn, 2007; Camilleri et al., 2014; Yan et al., 2015), and presbyopia (Durrie & McMinn, 2007; Polat et al., 2012). Performance in individuals with specialized skill sets like athletes (Clark et al., 2012; Deveau, Ozer, & Seitz, 2014), medical trainees (Krasne et al., 2013; Rimoin et al., 2015), and aviation professionals (Schneider, Vidulich, & Yeh, 1982; Kellman & Kaiser, 1994) also benefits from PL. Vision scientists have great interest in understanding PL more clearly not only because of its obvious utility in practical applications, but because it is an intriguing expression of experience-dependent plasticity in the adult brain that Wiesel & Hubel (1963) first described in the developing visual system.

One particularly interesting aspect of PL is its specificity to parameters employed in training, such that the benefits of learning do not fully generalize to conditions that were not experienced during training. For example, participants exhibit benefits of learning on a texture discrimination task when the target is presented to the location where training occurred, but not for other visual field locations (Karni & Sagi, 1991; Yotsumoto et al., 2008, 2009). In addition to retinotopic location (Shiu & Pashler, 1992), specificity of visual PL has been demonstrated for many features including spatial frequency (Fiorentini & Berardi, 1980; Sowden, Rose, & Davies, 2002), orientation (Fiorentini & Berardi, 1980; Ahissar & Hochstein, 1997), motion direction (Ball & Sekuler, 1987; Rokem & Silver, 2010, 2013), and ocularity (Karni & Sagi, 1991; Fahle, Edelman, & Poggio, 1995).

Such specificity is often interpreted to be indicative of changes in response properties of early visual cortical neurons that are tuned for the dimension along which specificity occurs. However, other factors such as attention (Ahissar & Hochstein, 1993), decision processes (Petrov, Dosher, & Lu, 2005), and reinforcement (Seitz & Dinse, 2007) are involved in PL, and it is also possible that PL's specificity reflects a change in the readout of early visual cortical activity by other areas (Dosher & Lu, 1999; Zhang et al., 2010). This hypothesis is supported by recent reports that double training (Xiao et al., 2008) and training-plus-exposure (Zhang et al., 2010) paradigms allow for the full benefits of learning to transfer to untrained conditions.

While great attention has been paid to pinpointing PL's neural loci, comparatively little has focused on understanding the neurochemical mechanisms of functional change. It has been suggested that the neurotransmitter acetylcholine (ACh) might play an important role in PL, based in

part on considerable neurophysiological evidence that ACh bolsters cortical sensory plasticity. Animal studies show that pairing electrical stimulation of the nucleus basalis – the chief source of cortical ACh – with stimulus presentation: 1) amplifies stimulus-evoked cortical responses (Rasmusson & Dykes, 1988; Metherate & Ashe, 1993; Hars et al., 1993; Takata et al., 2011) 2) triggers stimulus-specific modifications of cortical receptive field selectivity (Metherate & Weinberger, 1990; Bakin & Weinberger, 1996; Froemke et al., 2007) and 3) expands representations of the paired stimulus in cortical maps (Kilgard & Merzenich, 1998; Mercado et al., 2002). Similar experiments replacing nucleus basalis stimulation with direct application of ACh onto sensory cortical neurons reproduce these effects on responsiveness (Sillito & Kemp, 1983; Disney, Aoki, & Hawken, 2007), receptive field selectivity (Greuel, Luhmann, & Singer, 1988; Murphy & Sillito, 1991), and plasticity of sensory cortical maps (Penschuck et al., 2002). These findings suggest that increased cholinergic transmission facilitates sensory responses and the selection of specific stimuli from the environment, further augmenting plasticity in the populations of neurons representing these stimuli (Sarter et al., 2005; Rokem & Silver, 2010; Kang, Huppé-Gourgues, & Vaucher, 2014).

We have previously explored the effects of increased cortical ACh on experience-dependent plasticity in humans with sustained (multiple daily doses) administration of donepezil (brand name Aricept), a cholinesterase inhibitor, during visual PL (Rokem & Silver, 2010). Cholinesterase inhibitors increase synaptic ACh concentration by reducing its metabolic inactivation, thus preserving the qualitative nature of endogenous cholinergic signaling while quantitatively boosting it. Rokem & Silver (2010) found that sustained cholinergic enhancement amplified both the magnitude and the stimulus specificity of motion discrimination learning. This effect was enduring and was evident at least 15 months post-training and drug administration (Rokem & Silver, 2013).

In the current study, we asked if transient cholinergic enhancement with a single dose of donepezil would similarly facilitate PL of the location-specific texture discrimination task (Karni & Sagi, 1991). In a double-blind crossover design, we examined the time course of cholinergic effects on PL by evaluating texture discrimination performance 1 day, 2 weeks, or 4 weeks after training and drug/placebo administration. Each subject completed two training courses – one each for donepezil and placebo – in separate visual field locations (Figure 2.1A). We tested whether transient cholinergic enhancement would increase the extent and specificity of texture discrimination learning in a manner similar to sustained cholinergic enhancement.

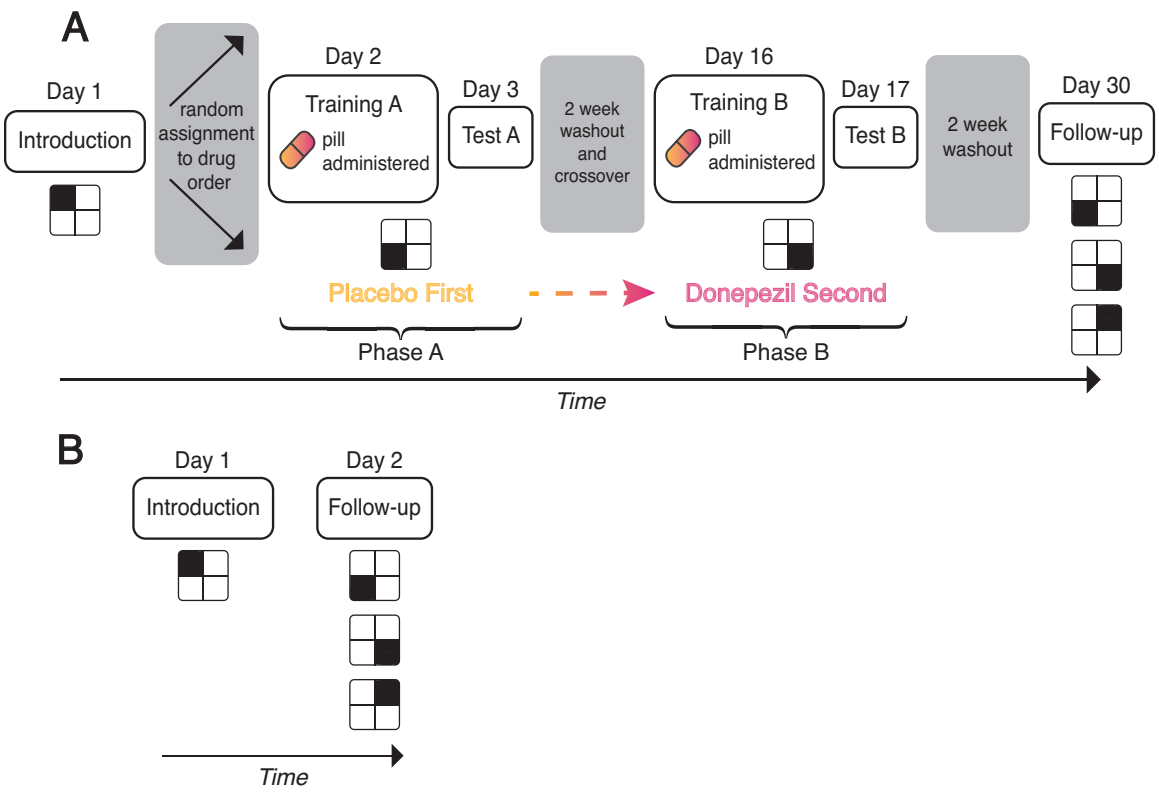


**Figure 2.1 Experimental procedure examples. A)** The main experiment consisted of six sessions: an initial introduction to the TDT, two pharmacology-paired trainings (Days 2 and 16; one each for donepezil and placebo), two next-day tests (Days 3 and 17), and a final follow-up (Day 30). Drug administration order, drug-to-quadrant pairing, and follow-up session run order were counterbalanced across subjects. In each panel, icons below each session indicate the visual field quadrants where testing occurred. **B)** The control experiment replicated the main experiment without the pharmacology-paired training and next-day testing sessions. It consisted of only the initial TDT introduction and the next-day, follow-up session. Run order was counterbalanced across subjects.

## 2.2 | Methods

### 2.2.1 | Participants

Twenty-six adults (17 females) with normal or corrected-to-normal vision volunteered for the main experiment. Six additional normally-sighted adults (5 females) participated in a subsequent control experiment. Exclusion criteria for both experiments included: 1) asthma or other respiratory problems; 2) habitual tobacco or psychoactive substance use; 3) any tobacco or psychoactive substance use in the past 30 days; 4) history of seizure; 5) cardiac irregularity; 6) use of any medications contraindicated for donepezil; and 7) pregnancy. All

procedures were conducted in accordance with the Declaration of Helsinki and were approved by the Committee for the Protection of Human Subjects at the University of California, Berkeley. Participants provided written informed consent and were compensated for their time.

### 2.2.2 | Texture Discrimination Task (TDT)

To perform the TDT, observers must discriminate both the orientation of a foreground texture target and the identity of a fixation target embedded in a patterned background of distractors (Figure 2.2, zoomed inset). The fixation target was a randomly oriented letter ("L" or "T"), and the texture target was a triplet of 45° bars that was aligned either horizontally or vertically. The fixation target was always presented centrally, while the position of the texture target varied within an arc extending from 2.5 to 5.9 degrees of visual angle from fixation. The background distractor elements were slightly and randomly jittered horizontal line segments arranged in a 19 x 19 grid. Within a run, the texture target appeared in only one visual field quadrant, and subjects were informed which quadrant would contain the texture target before each run began.

Subjects made two button press responses per trial. The first identified the centrally presented letter, and the second indicated the texture target orientation. Each trial (Figure 2) consisted of a fixation display (13.3 ms), a blank pre-stimulus interval (106.4 ms), the target display (26.6 ms), a blank interstimulus interval (ISI) of varying duration (details below), the mask (13.3 ms), and a second fixation display cueing the subject to respond (2000 ms). Following the response period, audiovisual feedback was provided for 250 ms.

Two varieties of the TDT were used throughout the study: a practice (suprathreshold) version, and a full (supra- to sub-threshold) version. Every block contained 25 trials of the same ISI duration. The block with the longest ISI was performed first; ISI values were then reduced with each successive block, increasing task difficulty. In the practice form of the task, 5 blocks were presented at ISIs of 997.5, 864.5, 731.5, 585.2, and 319.2 ms, for a total of 125 trials. The full version of the TDT consisted of 13 blocks, or 325 total trials, and employed ISIs of 598.5, 505.4, 399, 305.9, 252.7, 199.5, 159.6, 146.3, 119.7, 106.4, 66.5, 26.6, and 0 ms.

Stimuli were generated in MATLAB (The MathWorks Inc., Natick, MA, USA) via the Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997; Kleiner et al., 2007) and presented on a gamma-corrected 19-inch NEC (Minato, Tokyo, Japan) Multisync FE992 CRT display (mean luminance 59 cd/$m^2$) at a screen resolution of 1152 x 870 and refresh rate of 75 Hz. Participants used a chin and forehead rest to maintain a consistent seated position at a viewing distance of 60 cm in a dark, quiet room.

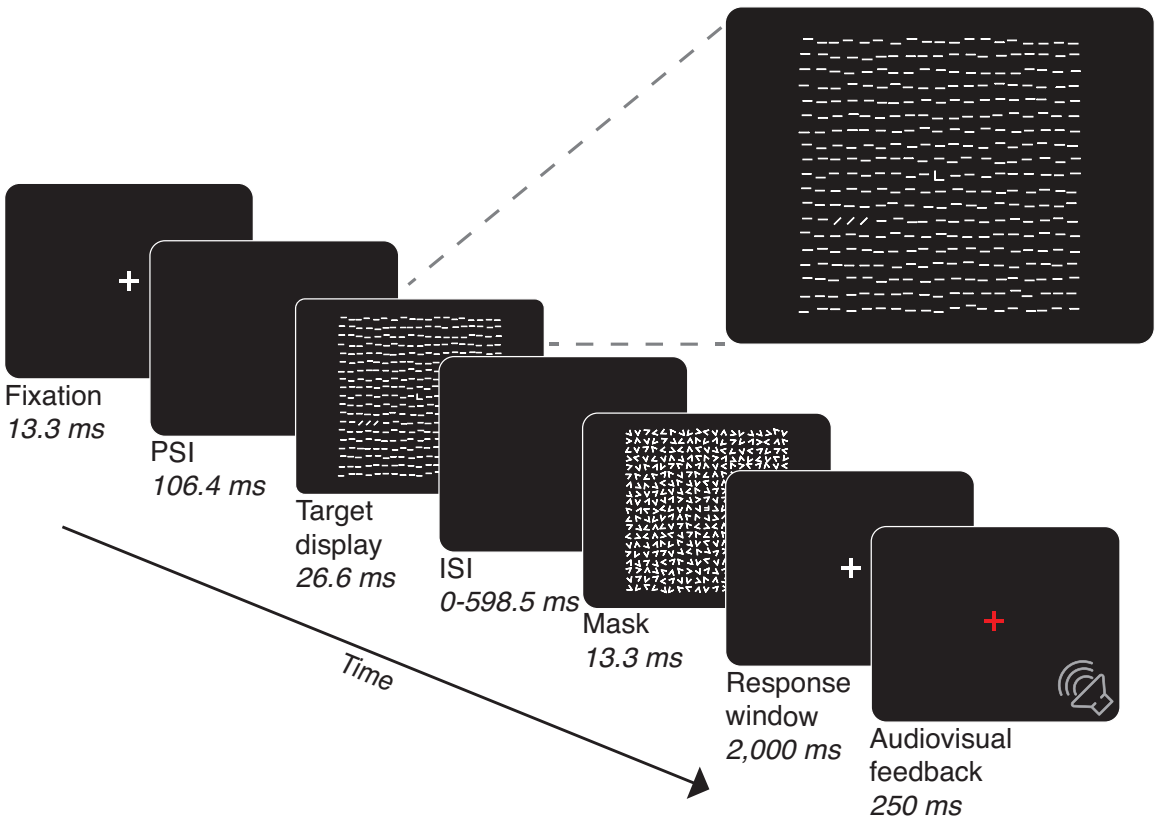


**Figure 2.2. Texture discrimination task trial sequence and target display**. Each trial began with a fixation cross, followed by a brief pre-stimulus interval (PSI). The target display was followed by an interstimulus interval (ISI) of variable duration. Importantly, ISI duration titrated task difficulty: as time between target offset and mask onset increased, the masking effect weakened, and task difficulty decreased. On each trial, participants were asked to indicate the fixation target identity and texture target orientation. **Zoomed inset.** The fixation and texture targets comprised the foreground elements of the target display: a centrally presented letter, 'L' (shown) or 'T,' and a peripheral triplet of 45° bars aligned horizontally (shown) or vertically.

### 2.2.3 | Procedure

The main experiment consisted of six sessions that were precisely spaced over 30 days (Figure 2.1A). In the first session (Day 1), participants were assessed on the practice version of the TDT to establish their understanding of and ability to perform the task. This introductory session was always conducted in the upper left quadrant of the visual field. To diminish the impact of non-perceptual learning (e.g., response key mappings) on our initial measurements, participants were required to achieve 80% correct discrimination of both the fixation and texture targets during this introductory session. All subjects met this

performance benchmark in 2 - 4 runs of the practice TDT. Performance from this introductory session was not analyzed further.

The five remaining sessions consisted of the first training and testing day pair (Phase A: Days 2 and 3), the second training and testing pair (Phase B: Days 16 and 17), and the follow-up assessment (Day 30). Subjects began each of these sessions by performing the practice version of the TDT in the upper left quadrant until reaching 80% correct performance on both the fixation and texture tasks. This required no more than two runs across all subjects and sessions.

During the training sessions (Days 2 and 16), 5 mg of either donepezil or placebo was administered in a double-blind design immediately after completion of practice blocks. Because mean plasma concentration of donepezil peaks roughly four hours after oral ingestion of a 5 mg dose (Rogers & Friedhoff, 1998), subjects waited three hours before performing the full version of the TDT. Participants were required to remain awake and in the laboratory during this waiting period. Following the TDT training session, participants were allowed to leave the lab and instructed to get a full night's sleep that evening. They returned the following day (Days 3 and 17) for the test sessions. After performing the initial practice run in the upper left quadrant, participants were given a brief 5-10 minute break. The full version of the TDT was then presented in the same location where training took place the previous day.

One pharmacology-paired training session was conducted in each of the lower left and lower right visual field quadrants. Drug administration order and the pairing of drug and visual field quadrant were counterbalanced across subjects. No further drug administration occurred during the testing sessions (Days 3 and 17); however, because the half-life of a 5 mg dose of donepezil is approximately 80 hours (Rogers & Friedhoff, 1998), significant concentrations were present in a subject's body the day after drug administration. To ensure that any effects of donepezil administration were confined to the specified training and testing session pair, both Phase A and Phase B, and Phase B and follow-up, were separated by 2 weeks, or more than four times the 80 hour half-life.

The follow-up and final session (Day 30) occurred either 2 (for Phase A) or 4 (for Phase B) weeks after training to assess the persistence of learning in the absence of any further pharmacological modulation. On this day, participants performed the full version of the TDT three times: once each in the untrained (upper right) and two trained (lower left and lower right) quadrants. The order of these three runs was counterbalanced across subjects. Following practice completion, participants were given a short rest before beginning the first run of the full TDT. Subjects were required to take another 5-10 minute break before beginning testing on the next visual field quadrant.

Training happened in the lower hemifield, while location-selectivity testing occurred in the upper hemifield. The validity of this design rests on the assumption that TDT performance is symmetric across the horizontal meridian. We conducted a control experiment to assess the veracity of our assumption. The control experiment was designed to replicate the main experiment without the training and pharmacology components. It comprised two sessions that took place on consecutive days: an introductory session (Day 1) and a follow-up

session (Day 2). Other than their closer proximity in time, these sessions replicated the introductory and follow-up sessions from the main experiment exactly (Figure 2.1B).

### 2.2.4 | Analysis

For each run of the full TDT, we calculated percent correct discrimination of the texture target's orientation as a function of ISI duration. A Weibull function was fitted to the data using maximum likelihood estimation with the Palamedes toolbox (Prins & Kingdom, 2018). Each function was described by four parameters: threshold (free), slope (free), guess rate (fixed at 0.5), and lapse rate (free within the bound of 0-0.1). To control for improper fixation, only blocks where fixation target discrimination was 80% or better were entered into the fitting procedure. The threshold ISI corresponding to 80% correct discrimination of the texture target was extracted from the fitted function and served as the performance measure for the session. Fits that resulted in threshold ISIs less than 13.3 ms (a single frame on our monitor) and those that were calculated from seven or fewer blocks were excluded from analyses (9/200; 4.5% of all fits).

Learning was defined as the decrease in threshold ISI duration at the trained location between sessions and was assessed as a function of training and drug condition in a mixed-model repeated measures analysis of variance (ANOVA) that included the within-subject factors of session (training vs. testing vs. follow-up) and drug (donepezil vs. placebo) and the between-subject factor of drug administration order (donepezil first vs. placebo first).

## 2.3 | Results

### 2.3.1 | Improvement in performance of the texture discrimination task with practice is specific to the trained location.

Visual perceptual learning occurred as expected: the ISI needed to achieve threshold performance in the trained location decreased following each training session (Figure 2.3). The average ISI decrease at the trained location between training and next day testing sessions, collapsed across drug conditions, was 23.4 ± 4.6 ms. From testing to follow-up, ISIs again decreased on average by 18.7 ± 4.6 ms at the trained location. Between training and the follow-up session 2 - 4 weeks later, the average threshold ISI duration at the trained location had decreased by 42.1 ± 6.3 ms. A mixed-model ANOVA (Greenhouse-Geisser corrected) revealed a significant main effect of session, $F(1,1.24)=22.6$, $p<0.001$. Post-hoc comparisons employing paired samples t-tests and Bonferroni correction for multiple comparisons indicated that each pairwise difference was also statistically significant (Figure 2.3): training – testing ($t=4.51$, $p<0.001$), testing – follow-up ($t=4.25$, $p=0.001$), training – follow-up ($t=5.17$, $p<0.001$).

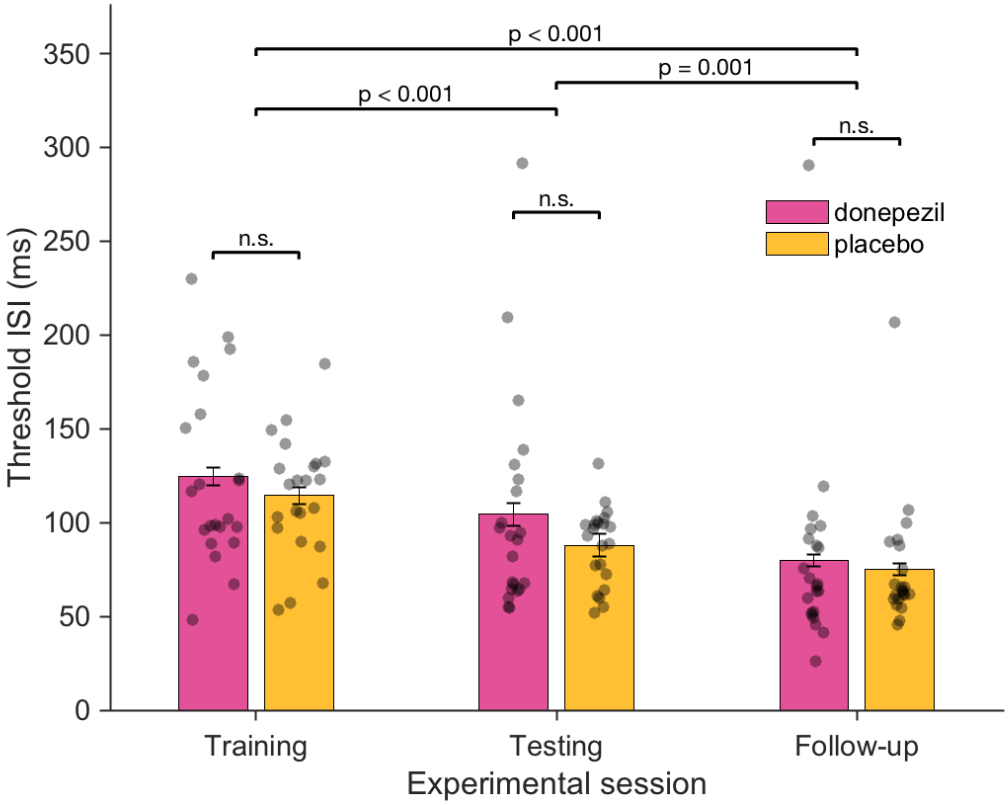


**Figure 2.3. Transient cholinergic enhancement did not affect task performance or the magnitude of perceptual learning.** Average threshold ISI durations for the donepezil and placebo conditions are plotted as a function of experimental session. Perceptual learning occurred in both drug conditions, as average threshold ISI decreased significantly from training to testing to follow-up. Moreover, pairing a single dose of donepezil with training did not boost these performance gains relative to placebo. Similarly, performance was not significantly different between the two drug conditions within any single session. Circles depict individual data points; error bars represent within-subject *SEM*.

We assessed the location specificity of perceptual learning by comparing each subject's average performance in the trained locations (one trained under donepezil and one under placebo) to their performance in the untrained location, all of which were measured during the follow-up session. The threshold ISI duration at the untrained location was 23.7 ± 6.3 ms longer than the threshold ISI at the trained locations, averaged over the donepezil and placebo conditions. A paired samples t-test indicated this difference was significant, $t(21)=3.75$, $p=0.001$, and thus, the full benefits of training did not transfer to the untrained upper right quadrant (Figure 2.4A). This result is consistent with the previously demonstrated location specificity of texture discrimination learning (Karni & Sagi, 1991; Yotsumoto et al. 2008, 2009).

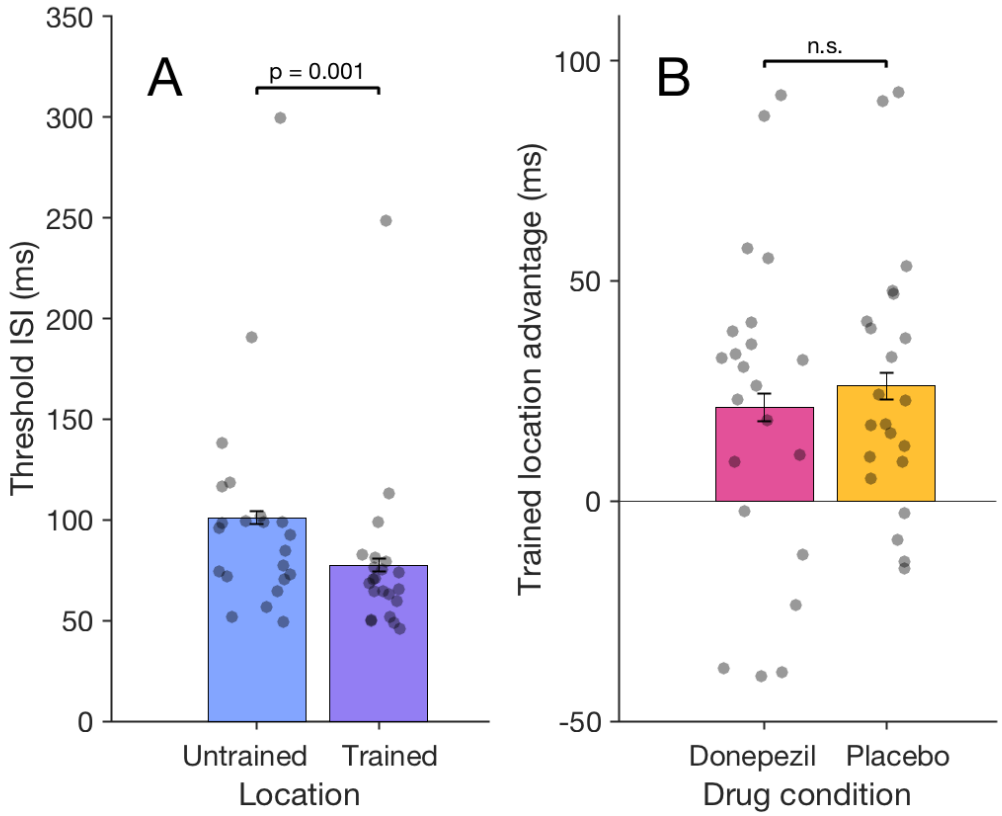


**Figure 2.4. The location specificity of texture discrimination learning is unaffected by transient cholinergic enhancement. A)** Texture discrimination learning is specific to the trained location. Average threshold ISI durations are plotted as a function of visual field location. In the follow-up session, the average ISI duration at the untrained location was significantly longer than the average ISI measured across the trained locations. In each panel, circles depict individual data points and error bars represent within-subject *SEM*. **B)** Transient cholinergic enhancement did not affect the location specificity of perceptual learning. The trained location advantage (difference in threshold ISI between the untrained and trained locations) at follow-up is plotted as a function of drug condition. The average donepezil-trained location advantage was not significantly different from the placebo-trained location advantage.

### 2.3.2 | Transient cholinergic enhancement increases neither the magnitude nor location specificity of texture discrimination learning.

To test the impact of transient cholinergic enhancement on both texture discrimination itself and on perceptual learning, we compared the donepezil and placebo conditions for both task performance and training effects. On average, collapsed across training, test, and follow-up sessions, threshold ISI durations in the donepezil condition were 10.6 ± 5.4 ms longer than in the placebo condition.

The ANOVA showed that this difference, represented by the drug factor, was not significant ($F(1,1)=1.9$, $p=0.179$), and that transient cholinergic enhancement neither improved nor impaired overall texture discrimination task performance compared to placebo (Figure 2.3).

The average ISI reduction at the donepezil-trained location from training to testing was 20.2 ± 7.9 ms. At follow-up, average ISI duration in the same quadrant had decreased by 24.6 ± 6.4 ms since testing and by 44.8 ± 9.6 ms since training. Between training and testing the average threshold ISI in the placebo-trained quadrant was reduced by 26.6 ± 4.9 ms and further decreased an additional 12.7 ± 6.5 ms between testing and follow-up. In the same location, the average ISI reduction was 39.4 ± 8.5 ms between placebo training and follow-up. The absence of a significant interaction between the drug and session factors in the ANOVA, $F(1,1.87)=1.2$, $p=0.308$, indicated that transient cholinergic enhancement did not enhance the magnitude of texture discrimination learning (Figure 2.3).

Again using data from the follow-up session, we separately contrasted performance in the donepezil- and placebo-trained quadrants with performance in the untrained quadrant to explore cholinergic effects on location specificity. The average difference in threshold ISI was 21.2 ± 7.8 ms between the untrained and donepezil trained quadrants, and 26.1 ± 6.2 ms between the untrained and placebo trained quadrants. A paired samples t-test showed this difference was not significant ($t(21)=0.79$, $p=0.438$), consistent with no effect of transient cholinergic enhancement on location specificity of texture discrimination learning (Figure 2.4B).

### 2.3.3 | Texture discrimination task performance is symmetric across the horizontal meridian.

In our study, training occurred in the lower visual field (LVF), while testing performance in a novel location was restricted to the upper visual field (UVF). This would pose a potential confound in our assessment of the location specificity of learning if texture discrimination task performance is asymmetric across the horizontal meridian. We are unaware of any evidence for such an asymmetry. Nevertheless, differences between the LVF and UVF in potentially relevant factors like spatial resolution (Carrasco, Talgar, & Cameron, 2001; Talgar & Carrasco, 2002; Abrams, Nizam, & Carrasco, 2012), attentional modulation (He, Cavanagh, & Intriligator, 1996; Kristjánsson & Sigurdardottir, 2008), and visual search (Previc & Naegele, 2001; Rezec & Dobkins, 2004) warrant further investigation of this matter.

To address a potential TDT performance disparity between the upper and lower hemifields, we conducted a second experiment in a group of naïve subjects. We structured this control experiment after the main experiment, but without the training and testing sessions (Figure 1B). This design allowed us to analyze data from the critical follow-up session both in isolation and in comparison to the same session from the main experiment. Our goal was to confirm that the differences observed at follow-up in the main experiment were

indeed due to training and not differences in UVF and LVF performance or the amount of hemifield exposure during follow-up.

Average threshold ISIs were similar across the three quadrants measured at follow-up in the control experiment: 129.4 ± 18.3 ms in the upper right, 135.3 ± 10.4 ms in the lower left, and 122.1 ± 9.9 ms in the lower right. A one-way repeated measures ANOVA exhibited no main effect of quadrant (upper right, lower left, and lower right; $F(5,2)=0.4$, $p=0.696$) on the untrained subjects' performance at follow-up, arguing against the existence of an inherent difference in texture discrimination between the LVF and UVF.

Finally, we examined the follow-up session data from both experiments as a function of experimental training and retinotopic location. Threshold ISIs from the lower left and lower right quadrants were averaged together to generate a single LVF threshold. A two-way ANOVA with factors of experimental group (main vs. control) and hemifield (UVF vs. LVF) showed a significant main effect of group ($F(1,52)=7.0$, $p=0.011$), but no effect of hemifield ($F(1,52)=0.7$, $p=0.422$). In addition, a paired samples t-test comparing control subjects' performance between the two hemifields did not show a significant difference ($t(5)=0.04$, $p=0.971$). While performance was significantly different between the UVF and LVF of the main subject group ($t(21)=3.75$, $p=0.001$), the results above support the conclusion that this difference is a result of their training in the LVF rather than a performance asymmetry in texture discrimination (Figure 2.5).

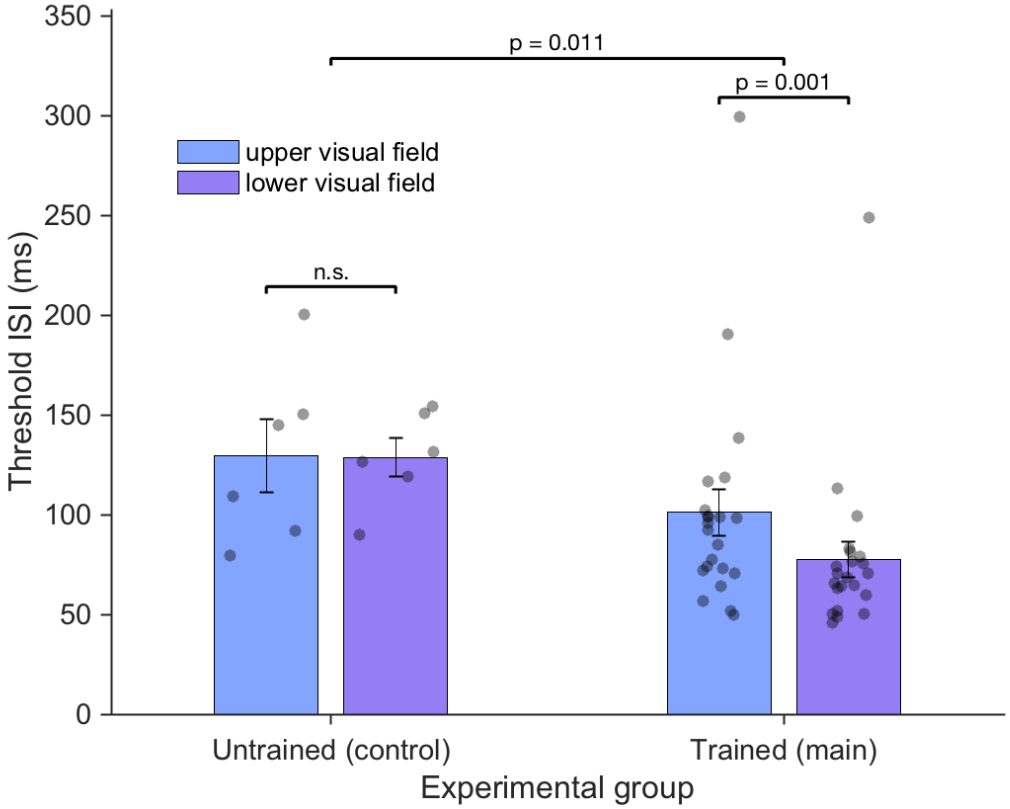


**Figure 2.5. Texture discrimination is symmetric across the horizontal meridian.** Average threshold ISI durations for the upper (UVF) and lower (LVF) visual fields are plotted as a function of experimental group. As expected, trained subjects' (main group) threshold ISIs are significantly shorter than those of untrained subjects (control group) in both locations. Similarly, trained subjects' performance in the trained location (LVF) is significantly better than in the untrained location (UVF). However, in the untrained group, performance is not significantly different between the two hemifields. Circles depict individual data points; error bars represent *SEM*.

## 2.4 | Discussion

We conducted a double-blind crossover study to examine the effects of transient cholinergic enhancement on perceptual learning of texture discrimination. Our training procedure significantly shortened threshold ISI durations when paired with a single dose of either donepezil or placebo. However, the magnitude of texture discrimination learning was unaffected by transient cholinergic enhancement. We also compared task performance in the trained lower visual field quadrants and the novel upper right quadrant and found that PL was location-specific, but also unaffected by transient cholinergic

enhancement. Finally, we conducted a control experiment to confirm that the observed location specificity was driven by training and not an inherent difference in texture discrimination ability across the visual field. We found no evidence of such an asymmetry, as texture discrimination performance between the UVF and LVF was indistinguishable in untrained subjects.

Our examination of PL offers a window into cortical plasticity beyond the critical period for typical visual development, which peaks by age four in humans (Banks, Aslin, & Letson, 1975). The susceptibility of neural circuits to restructure and change is markedly increased during this time compared to later in life, because the structural and functional brakes that restrict plasticity with maturity are largely unsolidified (Bavelier et al., 2010). During the critical period, molecules that hamper axonal growth are expressed at reduced concentrations (Pizzorusso et al., 2002), and the balance between excitatory and inhibitory cortical activity shifts most in favor of excitation (Hensch & Fagiolini, 2005). Neuromodulatory systems are effective regulators of excitatory-inhibitory balance, and deletion of the gene encoding for Lynx1 – a protein modulator of nicotinic ACh receptor function – was sufficient to induce ocular dominance plasticity in adult mice (Morishita et al., 2010).

The present study was motivated by recent findings in human observers indicating that the effects of sustained cholinergic enhancement, in which multiple drug administrations occurred over several days, on visual PL are complex and perhaps task-dependent. We previously reported that sustained cholinergic enhancement with donepezil increased the amount, rate, and specificity of motion discrimination learning compared to training under placebo (Rokem & Silver, 2010, 2013). Another study (Chamoun et al., 2017) found that combining training on a three-dimensional multiple object tracking task with repeated donepezil administration resulted in more rapid learning than training under placebo.

Based on reports of this nature, Chung et al. (2017) conducted a pilot study to explore the possibility that sustained cholinergic enhancement could similarly augment the therapeutic effects of PL on amblyopic vision. Despite employing a letter identification training protocol that had previously elicited PL in observers with amblyopia (Chung, Li, & Levi, 2012), and a donepezil administration schedule that had increased the rate and magnitude of PL of motion direction discrimination in normally sighted observers (Rokem & Silver, 2010), they found that sustained cholinergic enhancement decreased the rate of PL for single letter identification and completely blocked crowded letter identification learning. This finding reveals that cholinergic effects on plasticity can be task-dependent: donepezil had divergent effects on the same basic task (letter identification), in two different contexts (uncrowded and crowded) in the same observers. It also highlights that cholinergic effects on perceptual learning are not necessarily unidirectional: donepezil enhanced PL of motion-based tasks in normally sighted observers (Rokem & Silver, 2010, 2013; Chamoun et al., 2017) but impaired PL of letter identification tasks in observers with amblyopia (Chung et al., 2017), and had no observable effect on texture discrimination PL in the present study. One intriguing possibility, consistent with the findings

described above, is that cholinergic enhancement differentially modulates plasticity in the dorsal 'vision-for-action' and ventral 'vision-for-perception' streams. The emergence of dorsoventral differences in cholinergic receptor density as early in the processing hierarchy as V2 (Eickhoff et al., 2008) presents a possible functional substrate for such a finding. Future work in this area should explore this prospect further.

Because donepezil was administered throughout both training and testing in the studies discussed above, it is unclear which stage(s) of learning were impacted by increased ACh: initial stimulus processing (encoding), offline stabilization that occurs during both wake and sleep (consolidation), and/or retrieval. Beer and colleagues (2013) approached this problem by using nicotine, a rapidly metabolized nicotinic ACh receptor agonist, to isolate the effects of transient cholinergic enhancement on PL consolidation. After texture discrimination training, but prior to testing, subjects received either nicotine-rich chewing tobacco or an inactive control substance. Results showing greater texture discrimination learning in the drug group suggested that nicotine facilitated the magnitude of PL specifically by promoting its consolidation. This is consistent with the beneficial effects of rapid eye movement (REM) sleep on PL consolidation and maintenance (Karni et al., 1994; Stickgold et al., 2000; Mednick et al., 2003; McDevitt et al., 2015), as ACh release during sleep peaks in the REM stage (Jasper & Tessier, 1971; Marrosu et al., 1995).

The beneficial effect of transient cholinergic enhancement on PL of texture discrimination that was reported by Beer et al. (2013) appears to directly contradict our own finding of no effect of cholinergic enhancement by donepezil on this type of learning. However, given the fast-acting psychoactive effects of smokeless tobacco (Henningfield, Fant, & Tomar, 1997) it is possible that subjects became aware of their assignment to the treatment group during training, and that this inference contributed to their enhanced improvement.

We chose to use donepezil, rather than a cholinergic receptor agonist like nicotine, as cholinesterase inhibitors are arguably more physiologically relevant for studying the synaptic effects of endogenous ACh. This is because despite systemic administration, cholinesterase inhibitors only have a biochemical effect at those synapses that are releasing endogenous ACh. Cholinesterase inhibitors like donepezil therefore amplify the normal synaptic transmission at cholinergic synapses, unlike receptor ligands that indiscriminately activate or block cholinergic synapses of particular subtypes. In the study by Beer et al. (2013), nicotine administration could have improved task performance through other chemical pathways by activating presynaptic heteroreceptors that influence the release of other neuromodulators including dopamine, noradrenaline, glutamate, and GABA (Wonnacott, 1997). Nicotine also selectively facilitates excitatory synaptic transmission (McGehee et al., 1995) and is unlikely to impact excitatory-inhibitory circuit balance in the same manner as endogenous ACh release.

While Beer et al. (2013) demonstrated that nicotine administration increases consolidation of PL of texture discrimination, there is also reason to believe ACh could improve encoding of visual stimuli during learning. For example, disrupting cholinergic transmission with cortical deafferentation or

scopolamine (a muscarinic ACh receptor antagonist) blocks the encoding of novel perceptual information in both animals and humans (Naor & Dudai, 1996; Rosier et al., 1999; McGaughy et al., 2005). We timed our donepezil administration to occur three hours prior to the onset of training so that increased cholinergic tone would peak during encoding. However, since donepezil's terminal half-life is approximately 80 hours (Rogers & Friedhoff, 1998), ACh levels were elevated during the consolidation and retrieval processes as well. Despite this, we found that transient cholinergic enhancement did not facilitate PL of texture discrimination. Could it be the case that encoding during PL is unaffected by cholinergic enhancement? Evidence for facilitation of both sensory processing and attention by ACh argues against this suggestion.

In fact, one influential and well-supported model posits that high cortical cholinergic tone specifically augments encoding (Hasselmo, Anderson, & Bower, 1992; Hasselmo & McGaughy, 2004; Hasselmo & Sarter, 2011). One possibility is that ACh enhances encoding by amplifying the beneficial effects of endogenous attention on perception (Rokem et al., 2010). Physiology studies in animal models, where ACh can be directly applied to neurons in sensory cortex, also offer strong support for this theory. In macaque visual cortex, ACh application enhances thalamocortical (bottom-up) transmission and simultaneously inhibits horizontal and corticocortical (top-down) signaling (Disney, Aoki, & Hawken, 2007, 2012). Excitatory receptive field size is reduced by ACh application to marmoset visual cortical neurons (Roberts et al., 2005), consistent with greater influence of inputs from LGN neurons that have small receptive fields. Similarly, donepezil administration reduces the spatial extent of early visual cortical stimulus-evoked responses (Silver, Shenhav, & D'Espostio, 2008) and perceptual resolution (Kosovicheva et al., 2012; Gratton et al., 2017) in humans. Thus, cholinergic enhancement biases cortical circuit dynamics towards feedforward processing of extrinsic stimuli, and could be especially beneficial for encoding high spatial resolution information. Though we did not observe an effect of cholinergic enhancement on PL of texture discrimination, this could be because TDT performance was not limited by the spatial resolution of perception. Evidence that TDT learning is driven mostly by improved temporal segregation of the texture and mask displays, not enhanced spatial segregation of the texture target from the background, supports this assertion (Wang, Cong, & Yu, 2013).

It is also possible that design limitations could play a role in our null results. Participants varied in factors known to influence pharmacokinetics (e.g., body mass index), yet each subject received the same 5 mg dose of donepezil in our study. However, we have successfully measured effects on cortical function and perception employing this procedure several times before (Silver, Shenhav, & D'Esposito, 2008; Rokem et al. 2010; Kosovicheva et al., 2013; Gratton et al., 2017). It does however remain possible that individual differences in donepezil absorption and metabolism masked transient cholinergic effects on PL. It could also be the case that the scope of cholinergic enhancement induced by a single low dose of donepezil is insufficient to have a functional effect on plasticity in healthy young adults (Nathan et al., 2001).

However, a recent finding that a single 5 mg donepezil dose reduced the perceptual eye dominance plasticity triggered by a few hours of monocular deprivation (Sheynin et al., 2019) argues against this. While there is convincing evidence for cholinergic enhancement modulating visual cortical plasticity in humans, it is less clear that the underlying relationship is monotonic. We hypothesize that this function is more likely to resemble the inverted-U-shaped one, well known for describing the multifaceted relationship between dopamine and cognitive control (Cools & D'Esposito, 2011). Such a relationship could help account for the observed population- and context-dependence of cholinergic effects, and is largely supported by the relevant human neuroimaging literature (Bentley, Driver, & Dolan, 2011).

Our study also provides evidence against an asymmetry between the upper and lower visual hemifields in texture discrimination ability. Other perceptual asymmetries are known to exist along the vertical meridian, where smaller spatial resolution at equivalent eccentricities in the LVF versus UVF underlies a performance advantage along the meridian's lower half (Carrasco, Talgar, & Cameron, 2001; Talgar & Carrasco, 2002). The size of this asymmetry however, corresponds to roughly 1 additional degree of parafoveal eccentricity at its peak along the vertical meridian (Talgar & Carrasco, 2002) and decreases with increasing angular distance from the midline (Abrams et al., 2012). Given that the position of our texture target varied over 3.4 degrees eccentricity and in distance from the vertical meridian, it is unlikely this asymmetry would meaningfully impact TDT performance.

Pourtois et al. (2008), reported significant changes in performance and EEG activity following TDT training in the UVF but detected no such changes in a second group that trained in the LVF. However, we here, and others (Karni & Sagi, 1991; Mednick et al., 2003; Yotsumoto et al., 2009; McDevitt et al., 2015) have demonstrated texture discrimination learning in the LVF. Thus, our finding of symmetry in texture discrimination ability across the horizontal meridian is consistent with the existing literature. This suggests that the location-specificity of our results from the main experiment is in fact due to the specificity of PL itself.

### 2.5 | Summary

We found robust, location-specific PL of texture discrimination with training. Acute administration of a single dose of donepezil prior to training did not affect either the magnitude or the location specificity of texture discrimination learning compared to placebo. We also demonstrated that texture discrimination is symmetric across the horizontal meridian, confirming that the location specificity of PL was not due to a lower visual field performance advantage. Our results add to the growing body of evidence indicating that cholinergic effects on both cortical plasticity and perception are complex and non-monotonic.

# 3 | Sustained cholinergic enhancement facilitates visual perceptual learning of texture discrimination

## 3.1 | Introduction

In the experiment presented in Chapter 2, we found that pairing transient cholinergic enhancement with a brief course of TDT training modulated neither the magnitude nor location specificity of perceptual learning compared to placebo training. One study did find evidence of a beneficial effect of a single dose of nicotine on PL consolidation (Beer et al., 2013). Yet, studies of sustained cholinergic enhancement with donepezil have found that cholinergic facilitation of PL emerged only after the repeated pairing of drug administration and task performance over several days (Rokem & Silver, 2010), or weeks (Chamoun et al., 2017). Thus, it is possible that the absence of an effect of a single donepezil dose on TDT learning detailed in Chapter 2 stemmed from an insufficient amount of participant exposure to donepezil-paired training.

The work presented in this chapter aims to address this possibility directly. Here, we asked if sustained cholinergic enhancement with multiple doses of donepezil over multiple days would modulate visual perceptual learning of texture discrimination. We employed a double-blind crossover design to assess the effects of sustained pharmacological cholinergic enhancement on the magnitude and selectivity of texture discrimination learning. Each participant completed two training and testing sequences; one paired with 10 daily donepezil doses and the other coupled with 10 daily placebo doses, in different visual field quadrants (Figure 3.1). We examined if sustained cortical cholinergic enhancement would increase the extent or specificity of texture discrimination learning as it did for motion direction discrimination learning (Rokem & Silver, 2010).

Though not addressed here further, for the purposes of interpreting the selectivity of TDT learning, it is important to note that these data were collected as part of a larger double training study in which the same participants trained on another visual task in a different visual field location during both pharmacology-paired training and testing sequences. In a landmark study, Xiao et al., (2008) found that the full benefits of conventionally retinotopically-specific contrast discrimination learning transferred to a second location where observers had trained on an orientation discrimination task. Double training has also been shown to reduce the location specificity of other visual PL tasks including Vernier hyperacuity (Wang et al., 2012, 2014) and the TDT (Wang et al., 2013).

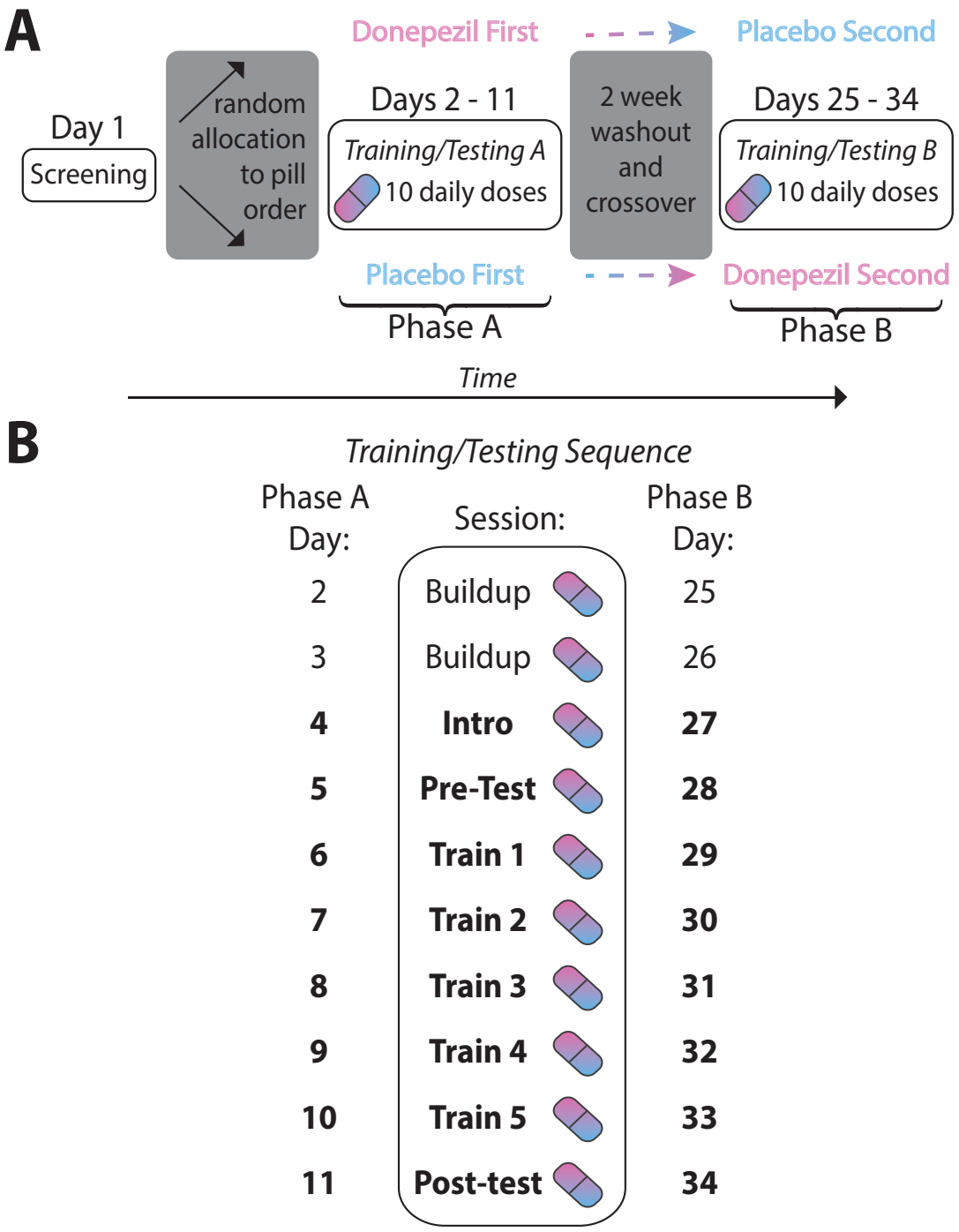


**Figure 3.1 Experimental procedure. A)** The experiment consisted of seventeen sessions: an initial screening visit and two pharmacology-paired, eight-session testing and training phases. Drug administration order, trained quadrant, trained background orientation, and the pairing of those three factors was counterbalanced across subjects within each phase. **B)** Each training/testing sequence included ten consecutive daily doses of either donepezil or placebo. Participants returned to the lab for assessment of texture discrimination task performance on the days in bolded print.

## 3.2 | Methods

### 3.2.1 | Participants

Eighteen healthy, right-handed adults (8 males; mean age 22.3 ± 0.8 years) volunteered to participate in the study. A LogMAR chart (Bailey & Lovie, 1976) was used to verify a binocular visual acuity of 0 (corresponding to 20/20 acuity on the Snellen chart) or better. Further information about these individuals is provided in Table 1. All subjects did not exhibit any of the exclusion criteria: 1) respiratory disease; 2) a history of consistent tobacco or psychoactive substance use; 3) any tobacco or psychoactive substance use in the previous 30 days; 4) epilepsy or seizure history; 5) cardiac problems; 6) prescription medication use contraindicated for donepezil; and 7) current pregnancy. All procedures were approved by the Committee for the Protection of Human Subjects at the University of California, Berkeley and were conducted under the principles set forth in the Declaration of Helsinki. All subjects provided verbal and written informed consent and received compensation for their time.

| Group | *N* (males) | Height (cm) | Weight (kg) | BMI ($kg/m^2$) | Age (years) |
|---|---|---|---|---|---|
| Donepezil-first | 9 (4) | 171.7 ± 3.8 | 67.9 ± 4.3 | 23.2 ± 1.7 | 22.3 ± 1.3 |
| Placebo-first | 9 (4) | 169.9 ± 2.0 | 63.6 ± 3.7 | 21.9 ± 0.9 | 22.3 ± 1.0 |

**Table 3.1 Demographic information for study participants.** Values in each of the last four columns are mean ± *SEM*.

### 3.2.2 | Texture Discrimination Task (TDT)

The same texture discrimination task used in our previous study (Chapter 2) was employed here, though its precise implementation differed in order to increase the proportion of near-threshold trials. Successful TDT performance requires that observers simultaneously discriminate the orientation of a peripheral target texture and the identity of a central letter within a patterned background (Figure 3.2, zoomed inset). The texture target was an array of three bars, each oriented at 45°, aligned either vertically or horizontally, and the fixation target was one of two randomly rotated capital letters: ‘T’ or ‘L’. The spatial position of the texture target changed location from trial to trial within an annulus spanning 2.5 – 5.9 degrees eccentricity from fixation, while the target letter was always presented at central fixation. The background components were short vertical or horizontal line segments organized along a 19 x 19 lattice with slight random spatial jittering.

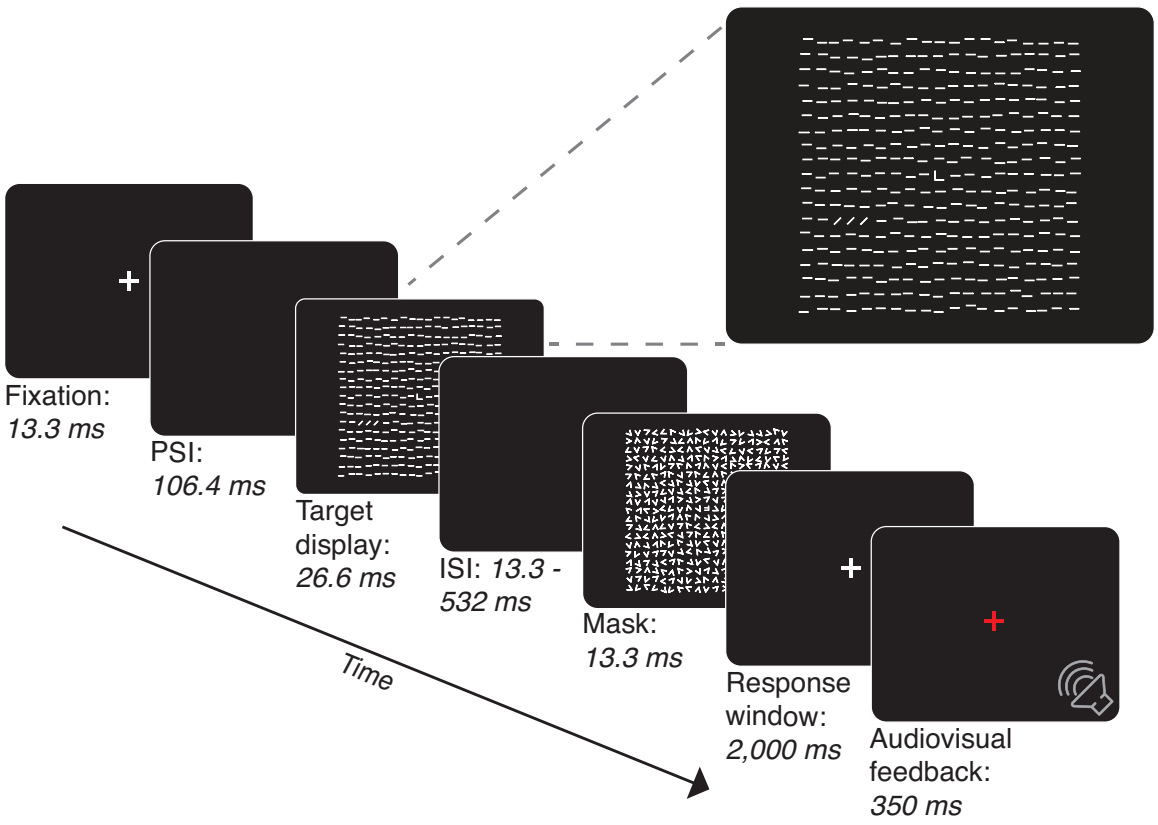


**Figure 3.2 Texture discrimination task trial sequence and target display**. Every trial began with a fixation cross and short pre-stimulus interval (PSI). The target display was flashed briefly and followed by a variable duration interstimulus interval (ISI) during which the screen remained blank. The mask display then appeared and was followed by the response window and performance feedback. ISI duration was adaptively varied by QUEST between trials. As ISI duration decreased, task difficulty increased. Observers were asked to discriminate both the identity of the fixation target and the orientation of the texture target. **Zoomed inset.** The fixation and texture targets respectively: a capital letter presented centrally, “L” (shown) or “T,” and a triplet of 45° bars presented peripherally and aligned either horizontally (shown) or vertically.

The texture target always appeared in the same visual field quadrant within a given block. An instruction appeared before the start of each block to inform observers which quadrant would contain the texture target. To provide their responses, participants made two button presses. The first indicated the identity of the fixation target while the second identified the orientation of the texture target.

Every block consisted of 50 trials which all employed the same background element orientation (Figure 3.2). The duration of the blank ISI controlled task difficulty and was varied adaptively by a QUEST psychophysical staircase (Watson & Pelli, 1983) converging on 80% correct performance. To control for improper fixation, only trials with correct letter identification were

entered into the staircase. The ISI for the first trial of the first block of each pre-test, post-test, and initial training staircase was 300 ms. After that trial, the algorithm varied the ISI from trial to trial within the bounds of 13.3 – 532 ms (corresponding to 1-40 frames on our display). The mean of the posterior probability distribution function was taken at the end of each block and served as both the threshold estimate for that block (Sims & Pelli, 1987; King-Smith et al., 1994) and the starting ISI for the following block of the same type. The ISI for the first trial of the first block of all remaining training days was the threshold estimate obtained from the final block of the previous training day.

Stimuli were created in MATLAB (The MathWorks Inc., Natick, MA, USA) with the Psychophysics Toolbox package (Brainard, 1997; Pelli, 1997; Kleiner et al., 2007) and presented on a gamma-corrected 19-inch ViewSonic (Brea, CA, USA) G90fb-2 CRT display at a screen refresh rate of 75 Hz and 1152 x 870 pixel resolution. Observers sat in a chin and forehead rest to maintain their position at a fixed 60 cm viewing distance in a dark, quiet room.

### 3.2.3 | Procedure

Our double-blind crossover design was modeled after previous studies in which we have explored the effects of cholinergic enhancement with donepezil on PL (Rokem & Silver, 2010; Chapter 2). The experiment consisted of 17 sessions that were strictly spaced in time (Figure 3.1A). In the screening session that occurred on Day 1, participants provided demographic information and received 10 pills with instructions for daily self-administration over the following 10 days. This period, Days 2 – 11, comprised the first of two pharmacology-coupled training/testing sequences (Figure 3.1B). The second training/testing sequence was structured identically and occurred two weeks later on experimental Days 25 – 34. Drug administration order was counterbalanced between subjects. The two sequences were separated by exactly two weeks, considerably longer than donepezil's 80-hour half-life (Rogers et al., 1998), in order to ensure elimination of the drug from the body following Phase A (if present) and to equate consolidation time of Phase A learning across individuals.

Participants did not return to the lab on buildup days (Days 2 – 3 and Days 25 – 26) but did self-administer a pill on each of these days, to allow the plasma concentration of donepezil (if present) to approach steady state levels before any task exposure occurred. Over the next eight consecutive days, subjects both self-administered a pill and returned to the lab for one of the introductory, testing, or training sessions.

The goal of the introductory session was to familiarize observers with the testing environment and proper task performance, in order to separate the effects of this procedural learning from our initial measurements of task performance. To this end, on Days 4 and 27, subjects performed an introductory version of the TDT, in which rather than being adaptively varied from trial to trial, the ISI was fixed at a suprathreshold value of 600 ms. The background element orientation presented in these trials matched the orientation to be used in the subsequent training. Observers were required to repeat a 100 trial run, in which 25 trials (half

a standard block) was presented to each of the four visual field quadrants, until they reached 80% correct discrimination of both the fixation and texture targets. In most instances (30/36 introductory sessions), subjects met this performance criterion in 1 or 2 runs, while 3-6 runs were required in the remaining cases. Performance during the introductory session was not analyzed further.

In the pre-training test that occurred on Days 5 and 28, we assessed baseline TDT performance. Subjects performed a total of 20 blocks, 5 for each of the conditions we measured. The blocks were pseudorandomly interleaved so that one of each condition was completed before the next of that same type was presented. These conditions differed in their pairing of the stimulus location and background orientation employed during training as follows: 1) trained orientation in the trained quadrant, 2) untrained orientation in the trained quadrant, 3) trained orientation in the untrained quadrant, and 4) untrained orientation in the untrained quadrant. The untrained background orientation was orthogonal to the trained one, and the quadrant diagonally across fixation from the trained one was designated the untrained location. The starting block type, quadrant, and background orientation used in training were counterbalanced across observers within each sequence. The trained/untrained quadrant pair and trained orientation were counterbalanced within observers.

During the training sessions (Days 6 – 10 and 29 – 33), observers performed 16 TDT blocks (800 trials) in which the texture target always appeared in the trained background orientation and in the trained quadrant. The final post-training test that occurred on Days 11 and 34 was designed to explore the effects of sustained cholinergic enhancement and training on both the magnitude and stimulus specificity of PL, and it exactly replicated that sequence's earlier pre-training test session.

### 3.2.4 | Analysis

At the conclusion of each 50-trial staircase, the threshold estimate was defined as the mean of the posterior probability distribution function for that block (Sims & Pelli, 1987; King-Smith et al., 1994). This procedure yielded five threshold estimates for each of the testing conditions and 16 threshold estimates for each training day. The median value of the threshold estimates for a condition or session was considered to be the threshold estimate for that condition/session.

Perceptual learning was operationally defined as a decrease in threshold ISI duration between testing sessions and was assessed as a function of training, the specific stimulus parameters presented during training, and drug condition in a mixed-model repeated measures ANOVA that included the within-subject factors of training (pre vs. post), drug (donepezil vs. placebo), quadrant (trained vs. untrained), and background orientation (trained vs. untrained) and the between-subject factor of drug administration order (donepezil first vs. placebo first).

Because this analysis of raw threshold ISIs is sensitive to absolute differences in task performance between individuals, we also calculated a

normalized measure of improvement, percent PL, in each condition for each subject according to the following formula:

$$\%\, PL = 100 \times (\, 1 - \frac{threshold_{\,post-training}}{threshold_{\,pre-training}}\,)$$

Positive % PL values correspond to better performance after training, while negative values indicate deterioration in performance after training.

## 3.3 | Results

### 3.3.1| Visual texture discrimination learning is specific to the trained background orientation but not to the trained quadrant.

Repeated training produced PL in the trained condition (when the texture target was presented in the trained location and in the trained background orientation), as anticipated (Figure 3.3). The average decrease in threshold ISI for the trained condition, collapsed across drug conditions, with training was 42.9 ± 5.2 ms. The ANOVA results confirmed that the main effect of training was significant $F(1,1)=134.8$, $p<0.001$.

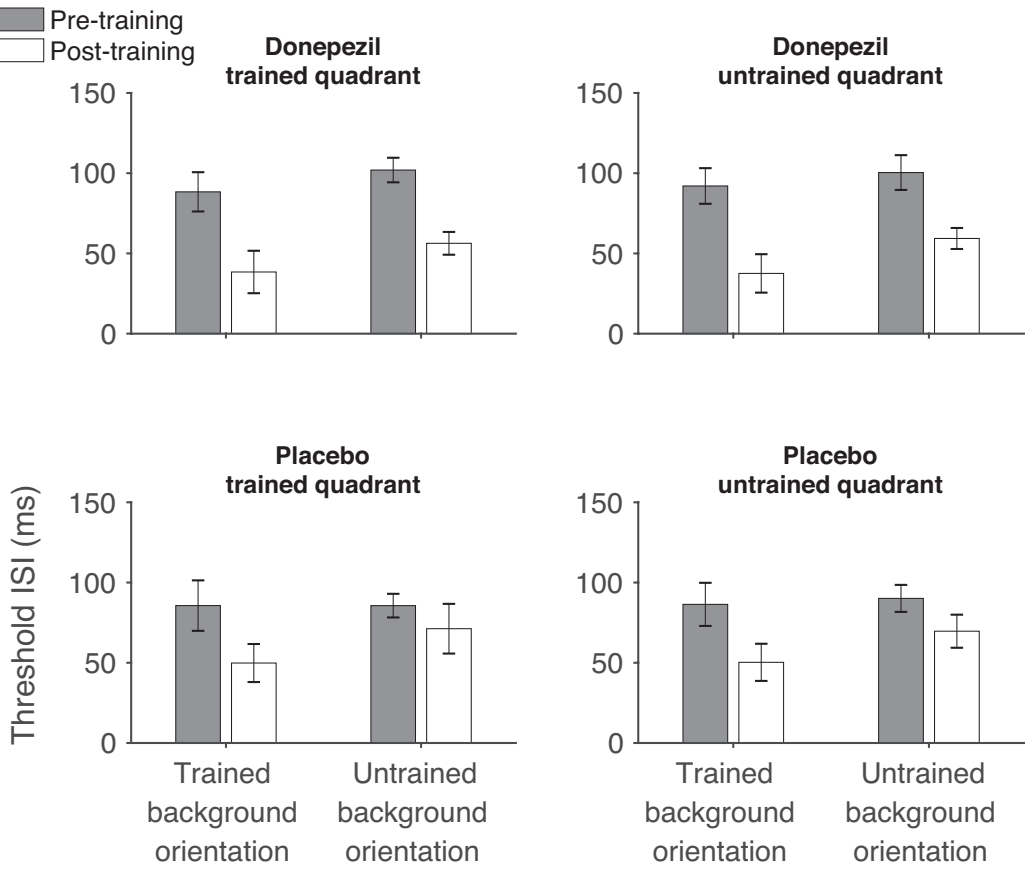


**Figure 3.3 The effects of sustained cholinergic enhancement and repeated training on texture discrimination task performance.** In each panel, threshold ISI durations before and after training are plotted as a function of the drug, visual field quadrant, and background orientation. Significant perceptual learning, a reduction in the ISI duration needed to elicit threshold performance post-training compared to pre-training, occurred in the trained condition. The magnitude of this learning was significantly greater when training was paired with sustained cholinergic enhancement, compared to placebo. Error bars denote within-subjects 95% confidence intervals.

To gauge the specificity of this learning, we compared the performance improvement in the trained condition to improvement in the condition where a parameter of interest was untrained. For example, location specificity was measured by subtracting the average ISI reduction in the untrained quadrant/trained background condition from the average ISI decrease in the trained quadrant/trained background condition. This difference was -2.4 ± 5.6 ms, and the interaction between quadrant and training as assessed by the ANOVA was not significant, $F(1,1)=0.2$, $p=0.680$, indicating that PL was not specific to the trained visual field location (Figure 3.3). Though TDT learning has been shown to be retinotopically specific (Karni & Sagi, 1991), there is evidence for transfer to other visual field locations following double training (Wang et al., 2013).

We examined PL's specificity to the trained background orientation in a similar fashion. The difference between the average ISI decrease in the trained quadrant/trained background condition and the same decrease in the trained quadrant/untrained background condition was 12.9 ± 7.1 ms. The ANOVA showed that the interaction between the training and background orientation factors was significant, $F(1,1)=4.5$, $p=0.049$, demonstrating that PL was specific to the trained background orientation (Figure 3.3). This is consistent with the previously reported specificity of texture discrimination learning for background element orientation (Karni & Sagi, 1991).

### 3.3.2 | Sustained cholinergic enhancement increased the magnitude, but not the specificity, of texture discrimination learning, compared to placebo.

We evaluated cholinergic effects on the magnitude of learning by directly comparing the improvement in the donepezil-trained and placebo-trained conditions (Figure 3.4). The average decrease in threshold ISI in the donepezil-trained condition was 49.9 ± 7.2 ms. In the placebo-trained condition, the same average reduction in threshold ISI duration was 35.8 ± 7.3 ms. This difference, represented in the ANOVA by the interaction between the drug and training factors, was significant, $F(1,1)=14.9$, $p=0.001$. The average PL magnitude was 52.3 ± 3.6 % under donepezil and 37.7 ± 4.8 % in the placebo condition. A paired samples t-test further confirmed that this difference was significant ($t=2.32$, $p=0.033$). This donepezil-induced increase in texture discrimination PL is consistent with our previous finding that sustained cholinergic enhancement increased the magnitude of motion direction discrimination PL (Rokem & Silver, 2010).

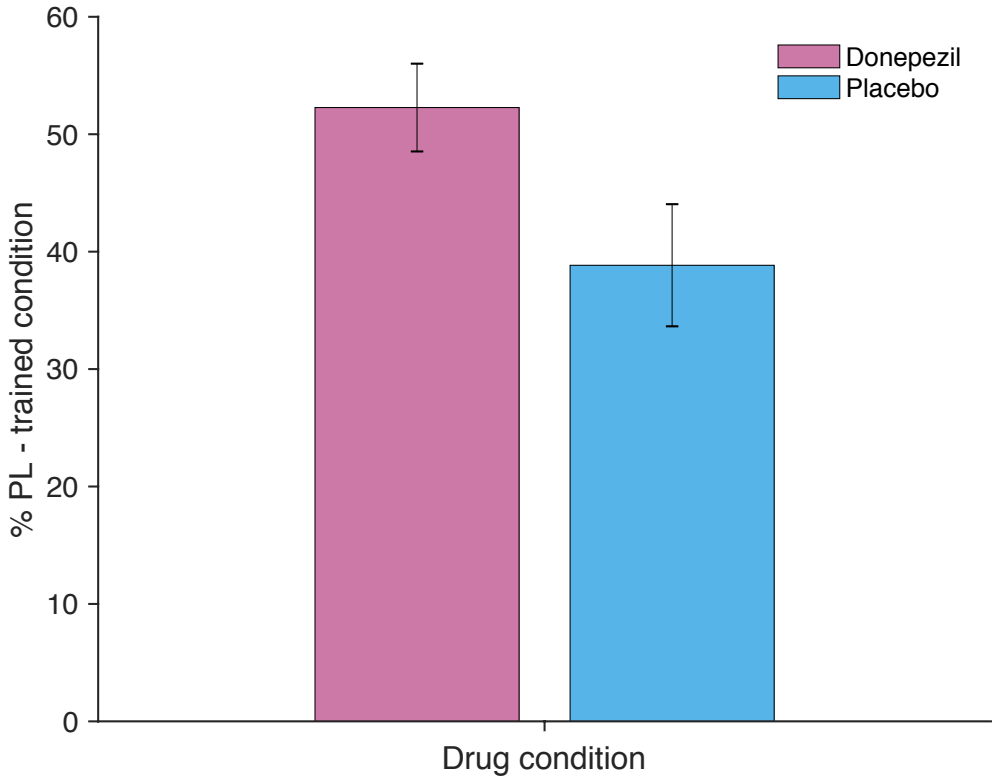


**Figure 3.4 Sustained cholinergic enhancement during training increases the magnitude of texture discrimination learning.** The amount of PL in the trained condition (texture target in the trained background orientation in the trained quadrant) is plotted as a function of drug condition. The magnitude of texture discrimination learning was significantly greater following donepezil training versus placebo training. Error bars denote the within-subjects 95% confidence intervals.

To examine the effects of sustained cholinergic enhancement on the location specificity of learning, we computed the same quadrant selectivity metric described above for the donepezil and placebo conditions separately. The average quadrant-specific threshold ISI reduction under donepezil was -4.6 ± 8.5 ms. The same average difference under placebo was -0.3 ± 7.4 ms. A paired samples t-test showed this difference was not significant ($t$=0.42, $p$=0.67). The absence of a cholinergic effect on PL's location specificity was confirmed by the normalized measure of learning. The average location specificity was -2.7 ± 4.4% under donepezil and -2.4 ± 4.8% under placebo. A paired samples t-test ($t$=0.04, $p$=0.971) again showed no significant difference in location specificity between drug conditions (Figure 3.5).

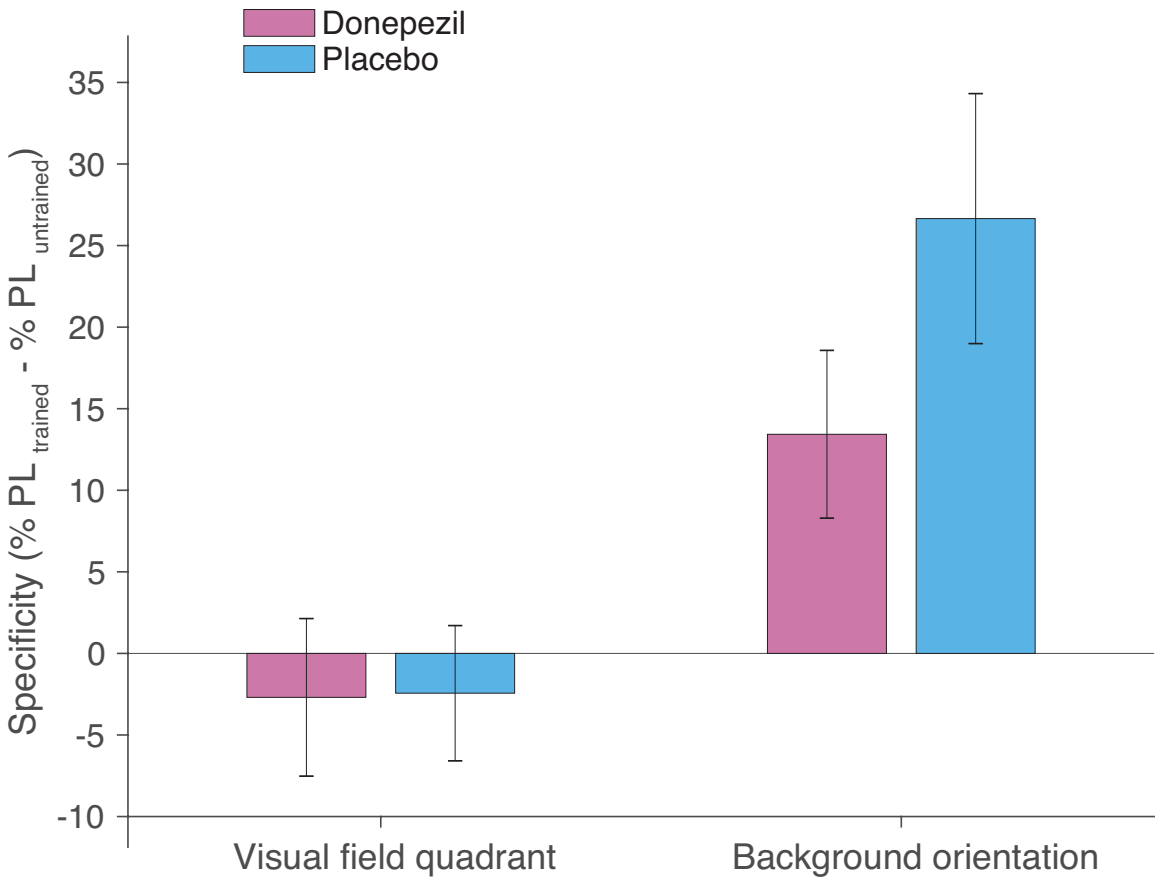


**Figure 3.5 Effects of sustained cholinergic enhancement on the specificity of texture discrimination learning.** The specificity of perceptual learning is plotted as a factor of the drug, quadrant, and background orientation parameters employed during training. Specificity for the parameter of interest was calculated by subtracting % PL in the condition where only that parameter was untrained from the fully trained condition. There was a trend toward less specific background orientation learning when training was paired with donepezil. However, sustained cholinergic enhancement did not significantly modulate either the location or background orientation selectivity of texture discrimination relative to placebo. Error bars denote the within-subjects 95% confidence intervals.

Sustained cholinergic enhancement tended to have a greater effect on the background element specificity of texture discrimination learning. The average background-orientation-selective ISI duration decrease was 4.3 ± 9.3 ms under donepezil and 21.4 ± 10.7 ms under placebo. Comparison of these values with a paired samples t-test showed that donepezil tended to decrease the background orientation specificity of PL compared to placebo ($t$=1.9, $p$=0.077). The average background-specific normalized improvement under donepezil was 13.4 ± 5.4 %, while under placebo this same value was 26.7 ± 10.0 % (Figure 3.5). A paired samples t-test revealed that this difference was not significant, $t$=1.4, $p$=0.191. The absence of a significant cholinergic effect on texture discrimination learning's

specificity is inconsistent with the enhanced directional specificity of motion discrimination learning reported by Rokem & Silver (2010).

### 3.4 | Discussion

We conducted a double-blind crossover study to explore the impact of sustained cholinergic enhancement on visual texture PL. Our training paradigm substantially reduced threshold ISI duration in the trained condition when paired with a 10 day course of either placebo or donepezil. The magnitude of this texture discrimination learning was significantly increased by sustained cholinergic enhancement compared to placebo. We also compared performance in the trained and untrained conditions to assess cholinergic effects on the selectivity of learning and found no significant cholinergic effects on either texture learning's location or background orientation specificity.

This study was driven by findings presented in Chapter 2, namely, that transient enhancement of endogenous cholinergic activity had no measurable effect on the magnitude of PL when paired with a short course of texture discrimination training. Here, we asked if combining a more sustained period of endogenous cholinergic enhancement with additional behavioral training would facilitate texture discrimination learning. In a prior study, Rokem & Silver (2010) found that sustained cholinergic enhancement boosted the magnitude of motion direction discrimination learning. It is apparent however, that this cholinergic benefit emerged only after several days of drug administration and task performance (Rokem & Silver, 2010; see Figure 4). Similarly, the beneficial effects of repeated donepezil administration and task practice on three-dimensional multiple object tracking learning were only evident after several paired sessions (Chamoun et al., 2017; see Figure 1). Though we did not observe any significant impact of transient cholinergic enhancement on texture PL in Chapter 2, the results described above suggest that this could be because the duration of combined cholinergic enhancement and TDT training employed was insufficient.

In the present study, we found that sustained cholinergic enhancement and a more substantial training protocol significantly increased TDT learning compared to placebo. This is consistent with the finding that a single training session followed by nicotine administration increased TDT learning, without affecting its specificity, when measured the following day (Beer et al., 2013). At the conclusion of our first study, participants had received one donepezil dose and completed 975 TDT trials (excluding the introductory session) in the donepezil-trained location (Chapter 2). By the conclusion of this study, subjects had received ten donepezil doses and completed 4,500 trials (excluding the introductory session) in the donepezil-trained quadrant. This supports the suggestion that our earlier null results stem from an inadequate amount of task exposure while cortical ACh levels were augmented.

Acetylcholine is broadly implicated in sensory plasticity and specifically in facilitating high precision sensory signal processing (Sarter et al., 2005; Furey, 2011). Repeated pairing of electrical stimulation of rat basal forebrain with visual

stimulation by an oriented grating improves visual acuity (measured by water maze performance) in an orientation-specific manner, and increases VEP amplitude in V1 (Kang et al., 2014b; Kang, Huppé-Gourgues, & Vaucher, 2015). In primate visual cortex, ACh potentiates thalamocortical afferents and suppresses corticocortical connections (Disney et al., 2007; 2012) and decreases excitatory receptive field size (Roberts et al., 2005). In humans, cholinergic enhancement with donepezil reduces the spatial spread of excitatory fMRI responses in early visual cortex (Silver, Shenhav, & D'Esposito, 2008) and the magnitude of surround suppression, as measured behaviorally (Kosovicheva et al., 2012) and enhances the spatial resolution of visual perception (Gratton et al., 2017).

These findings are consistent with the hypothesis that ACh benefits PL by augmenting learning-dependent re-tuning of the neuronal population representing the learned stimuli (Rokem & Silver, 2010; Kang et al., 2014a). Here, however, we found that cholinergic potentiation of PL was not specific to either the trained location or the trained background orientation. This suggests that enhanced plasticity specifically in those neurons that represent the trained stimuli is unlikely to be the primary mechanism mediating the cholinergic facilitation of learning reported here. It is important to note that ACh can also bolster visual cortical plasticity by increasing visual responses in a non-stimulus-specific manner (Bear & Singer, 1986; Bröcher, Artola, & Singer, 1992; Kang & Vaucher, 2009). This type of mechanism for cholinergic increases in the magnitude of visual texture discrimination PL is consistent with the findings reported by Beer et al. (2013), and with those presented here.

Cholinergic enhancement could also have facilitated PL by enhancing the beneficial effects of endogenous attention on perception and/or learning. Lesions to the basal forebrain impair attentional performance (Muir et al., 1993; Muir, Everitt, & Robbins, 1994; Voytko et al., 1994). Cortical ACh release increases during sustained visual attention (Passetti et al., 2000; Arnold et al., 2002), and cholinergic enhancement with donepezil augments the benefits of endogenous attention on visual perception (Rokem et al., 2010). Though endogenous attention is not a prerequisite for perceptual learning (Watanabe, Náñez, & Sasaki, 2001; Seitz & Watanabe, 2009), attending to the training stimulus can augment visual PL (Ito, Westheimer, & Gilbert, 1998; Li, Piëch, & Gilbert, 2004; Roelfsema et al., 2010).

A final mechanism to consider for the effects of endogenous cholinergic enhancement on PL is memory consolidation. There is direct evidence that increased cholinergic signaling following nicotine administration facilitates the consolidation of TDT learning (Beer et al., 2013). Texture discrimination learning consolidation also benefits from sleep, particularly from the REM stage (Karni et al., 1994; Stickgold et al., 2000), during which cortical ACh release peaks (Jasper & Tessier, 1971; Marrosu et al., 1995). Donepezil lengthens the duration of the REM stage in healthy adults (Nissen et al., 2006). Scopolamine, a muscarinic ACh receptor antagonist, specifically impairs the initial storage and maintenance of visual short-term memories (Aigner, Walker, & Mishkin, 1991; Robbins et al., 1997). Determining how to disentangle and study the separate effects of ACh on

response amplitude, attention, and consolidation of PL remains a challenging and important goal for future work.

An additional proposal, raised earlier in our discussion of the study presented in Chapter 2, is that cholinergic enhancement might affect plasticity in the ventral 'vision-for-perception' and dorsal 'vision-for-action' pathways differently. While increased cortical ACh levels increased the rate and extent of PL for motion-based tasks in normally sighted subjects (Rokem & Silver, 2010; Chamoun et al., 2017), they decreased or blocked PL of letter identification tasks in participants with amblyopia (Chung et al., 2017). Though spatial-resolution-limited texture discrimination is likely to be mediated primarily by ventral stream processing, TDT learning is chiefly temporal in nature (Wang et al., 2013). Additional experiments are required to clarify how cholinergic enhancement influences PL for tasks that are motion-based versus object- or location-based.

### 3.5 | Summary

We found that the magnitude, but not location or background orientation selectivity, of texture discrimination learning increased significantly when training was coupled with sustained donepezil administration. These results suggest that an increase in stimulus-specific plasticity is unlikely to be the biological mechanism supporting the improvements in PL with sustained cholinergic enhancement. Other possibilities consistent with the present findings are increased visual response gain, improved attentional allocation, augmented consolidation, or some combination of these factors.

## 4 | Conclusion

In this dissertation, I have addressed how pharmacological enhancement of endogenous cortical cholinergic signaling modulates the extent and selectivity of texture discrimination learning. Because these studies employed within-subject, double-blind, and placebo-controlled behavioral pharmacology designs, I was able to address questions about the neurochemistry of cortical plasticity in behaving healthy humans *in vivo*. This is significant, as these questions are most often explored with invasive methods that are suitable only for animal models or human patients.

Chapter 2 explored the effects of transient cholinergic enhancement on a brief TDT training course. Behavioral training yielded significant, location-specific PL. A single dose of donepezil, administered before training, impacted neither the magnitude nor location specificity of texture discrimination learning compared to placebo. To verify that the location specificity of PL was due to training and not a lower visual field performance advantage, a control experiment was performed. The results confirmed that TDT performance is symmetric across the horizontal meridian. While these null results do not support the hypothesis that endogenous cholinergic enhancement augments PL's magnitude, it is possible that a more prolonged and/or substantial course of drug administration and/or training would facilitate texture discrimination learning.

To address this possibility, Chapter 3 assessed the impact of sustained cholinergic enhancement on a more substantial TDT training schedule. The magnitude, but not selectivity, of texture discrimination PL significantly increased with donepezil training. These results suggest that augmented plasticity in the neuronal population representing the trained stimuli is unlikely to be the biological mechanism mediating cholinergic effects on PL. Other prospective mechanisms consistent with the study's findings are that cholinergic enhancement enlarged visual response amplitudes, enriched attentional allotment, enhanced memory consolidation, or some combination of these elements.

Many fundamental questions about cholinergic and other neurochemical effects on perceptual learning and sensory cortical plasticity remain unanswered. The studies presented here highlight the promise and feasibility of using behavioral pharmacology to further explore these questions in humans directly. Future studies should employ a combination of pharmacological tools and perceptual learning to continue developing our understanding of and ability to meaningfully leverage plasticity in the human brain.

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