

# Transient cholinergic enhancement does not significantly affect either the magnitude or selectivity of perceptual learning of visual texture discrimination

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Perceptual learning (PL), often characterized by improvements in perceptual performance with training that are specific to the stimulus conditions used during training, exemplifies experience-dependent cortical plasticity. An improved understanding of how neuromodulatory systems shape PL promises to provide new insights into the mechanisms of plasticity, and by extension how PL can be generated and applied most efficiently. Previous studies have reported enhanced PL in human subjects following administration of drugs that increase signaling through acetylcholine (ACh) receptors, and physiological evidence indicates that ACh sharpens neuronal selectivity, suggesting that this neuromodulator supports PL and its stimulus specificity. Here we explored the effects of enhancing endogenous cholinergic signaling during PL of a visual texture

discrimination task. We found that training on this task in the lower visual field yielded significant behavioral improvement at the trained location. However, a single dose of the cholinesterase inhibitor donepezil, administered before training, did not significantly impact either the magnitude or the location specificity of texture discrimination learning compared with placebo. We discuss potential explanations for discrepant findings in the literature regarding the role of ACh in visual PL, including possible differences in plasticity mechanisms in the dorsal and ventral cortical processing streams.

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## 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 (Watanabe & Sasaki, 2015; Doshier & Lu, 2017). Visual PL has been used therapeutically to treat 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, such as athletes (Clark et al., 2012; Deveau, Ozer, & Seitz, 2014), medical trainees (Krasne et al., 2013; Rimoïn et al., 2015), and aviation professionals (Schneider, Vidulich, & Yeh, 1982; Kellman & Kaiser, 1994), also improves following PL. There has been great interest in understanding PL not only because of its clear utility in practical applications, but also because it is an intriguing expression of the experience-dependent plasticity in the adult brain that Wiesel and Hubel (1963) described in the developing visual cortex.

Specificity of visual PL has been demonstrated for many stimulus features, including retinotopic location (Karni & Sagi, 1991; Shiu & Pashler, 1992; Mednick, Nakayama, & Stickgold, 2003), orientation (Fiorentini & Berardi, 1980; Ahissar & Hochstein, 1997), motion direction (Ball & Sekuler, 1987; Rokem & Silver, 2010; Rokem & Silver, 2013), and ocularity (Karni & Sagi, 1991; Fahle, Edelman, & Poggio, 1995). Such specificity has often been interpreted as reflecting changes in response properties of visual cortical neurons that are tuned along the dimension for which specificity occurs (Schoups et al., 2001; Schwartz, Maquet, & Frith, 2002; Yang & Maunsell, 2004; Yotsumoto et al., 2008; Yotsumoto et al., 2009; Ahmadi et al., 2018). However, other factors, such as attention (Ahissar & Hochstein, 1993), decision (Petrov, Doshier, & Lu, 2005), and reinforcement (Seitz & Dinse, 2007), are also involved in PL, and it is possible that at least some aspects of the specificity of PL reflect a change in the readout of early visual cortical activity by other areas (Doshier & Lu, 1999). This is supported by reports that double training (Xiao et al., 2008) and training-plus-exposure (Zhang et al., 2010) paradigms allow the full benefits of learning to generalize to novel conditions.

Although our knowledge of visual PL has advanced greatly (Sagi, 2011; Watanabe & Sasaki, 2015; Doshier & Lu, 2017), many fundamental aspects remain poorly understood. One of these is the ways in which neuromodulators shape PL (Roelfsema, van Ooyen, & Watanabe, 2010). We have previously explored the effects of enhancing cortical acetylcholine (ACh) signaling on visual PL in healthy humans by administering donepezil, a cholinesterase inhibitor

(Rokem & Silver, 2010). Cholinesterase inhibitors increase the synaptic concentration of ACh by reducing its metabolic inactivation. Because donepezil only affects activity at synapses at which ACh has been endogenously released, it preserves the pattern of naturally occurring cholinergic signaling while quantitatively boosting it. Rokem and Silver (2010) found that cholinergic enhancement amplified both the magnitude and the direction specificity of PL of motion direction discrimination. This effect was still evident at least several months after the completion of training and drug administration (Rokem & Silver, 2013).

The texture discrimination task (TDT) (Karni & Sagi, 1991) has been extensively studied and is one of the best-characterized visual PL tasks. Texture discrimination learning is specific to the trained location, background element orientation, and eye (Karni & Sagi, 1991). Only one previous study has investigated cholinergic modulation of TDT learning. A group of observers that chewed tobacco (containing nicotine, a nicotinic ACh receptor agonist) after TDT training showed significantly greater, but not more specific, PL compared with a control group (Beer, Vartak, & Greenlee, 2013). This study demonstrated that nicotine administration could enhance consolidation of texture discrimination learning. However, the role of endogenous ACh in the expression of PL of texture discrimination is still unclear, as unlike cholinesterase inhibitors, nicotine binds and activates ACh receptors even at synapses that have not endogenously released ACh, thereby qualitatively altering the landscape of cholinergic transmission.

In the current study, we asked if transient enhancement of endogenous cholinergic transmission with a single dose of donepezil would facilitate PL of texture discrimination. 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, and 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 1A). We tested whether cholinergic enhancement of endogenous signaling would increase the magnitude and specificity of texture discrimination learning in a manner similar to that previously described for motion direction discrimination learning (Rokem & Silver, 2010).

## Methods

### Participants

Twenty-six adults (17 women) with normal or corrected-to-normal vision participated in the main

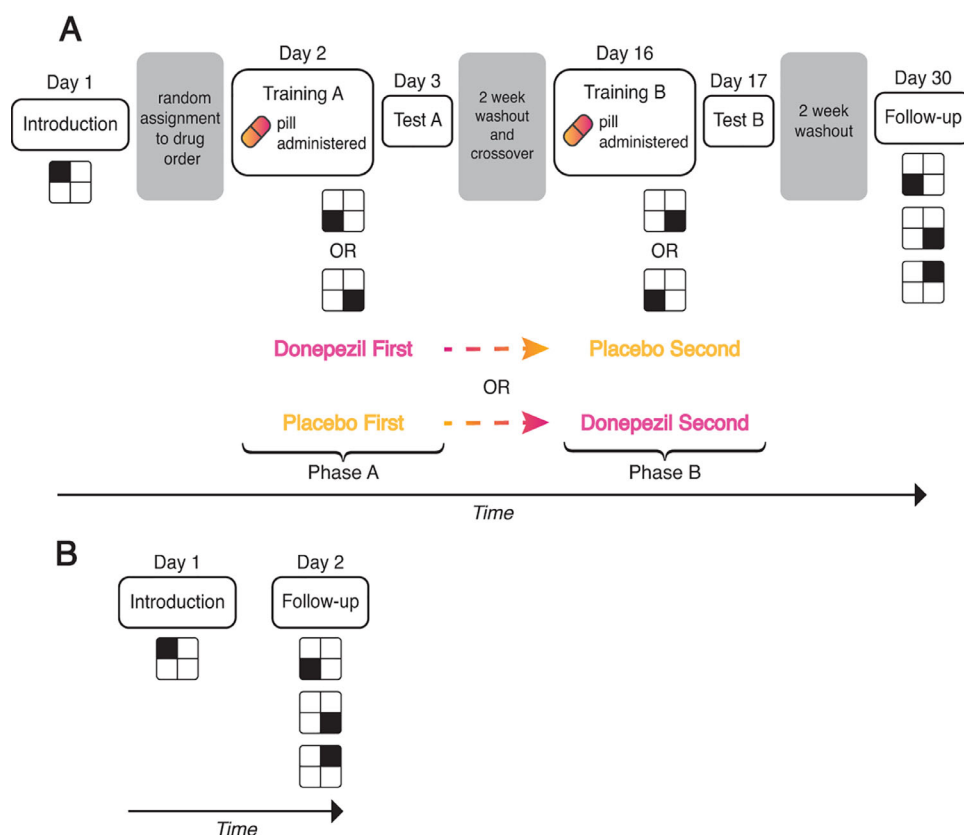


Figure 1. Experimental procedures. (A) The main experiment consisted of six sessions: an initial introduction to the TDT, two pharmacology-paired trainings (days 2 and 16; one each for donepezil and placebo), two next-day tests (days 3 and 17), and a final follow-up (day 30). Drug administration order, drug-to-quadrant pairing, and run order in the follow-up session 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 but did not include 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.

experiment. Six additional normally sighted adults (five women) participated in a subsequent control experiment. Exclusion criteria for both experiments included: (a) asthma or other respiratory problems; (b) habitual tobacco or psychoactive substance use; (c) any tobacco or psychoactive substance use in the past 30 days; (d) history of seizure; (e) cardiac irregularity; (f) use of any medications contraindicated for donepezil; and (g) 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.

## Texture discrimination task

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 on each trial (Figure 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, whereas the position of the texture target varied within an arc extending from 2.5° to 5.9° 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 prestimulus interval (106.4 ms), the target display (26.6 ms), a blank interstimulus interval (ISI) of varying duration (details later), the mask (13.3 ms), and

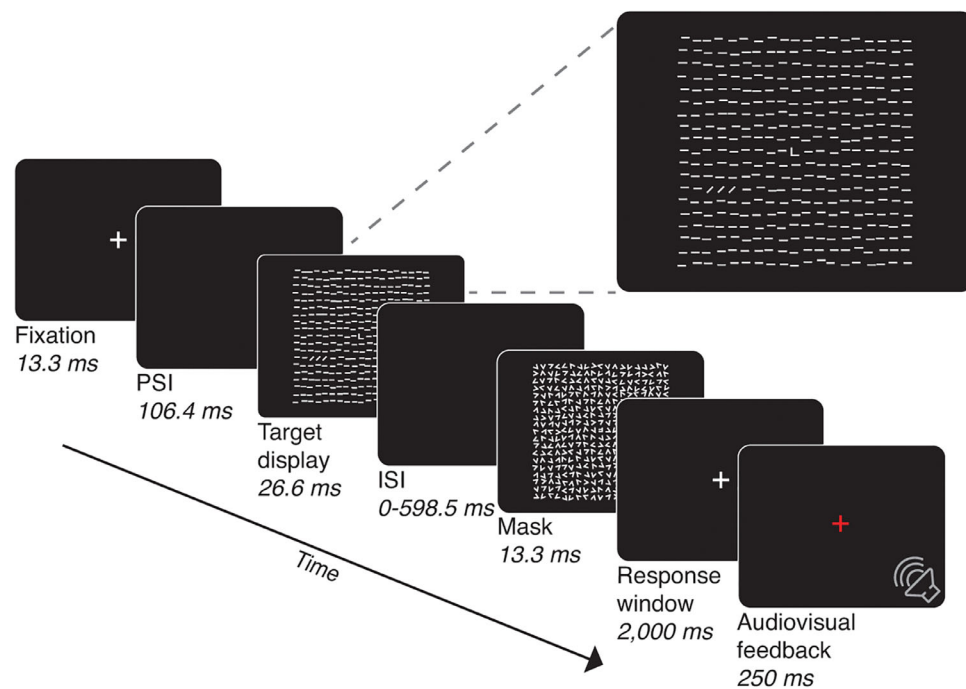


Figure 2. TDT trial sequence and target display. Each trial began with a fixation cross, followed by a brief prestimulus interval (PSI). The target display was followed by an ISI of variable duration. Importantly, ISI duration titrated task difficulty: as time between target offset and mask onset increased, the masking effect weakened, and task difficulty decreased. On each trial, participants were asked to indicate both 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.

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 subthreshold) 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 version of the task, five 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) with the Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997; Kleiner et al., 2007) and presented on a gamma-corrected 19-in. NEC (Minato, Tokyo, Japan) Multisync FE992 CRT display (mean luminance 59 cd/m<sup>2</sup>) at a screen resolution of 1152 × 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.

## Procedure

The main experiment consisted of six sessions over 30 days (Figure 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-PL (e.g., learning response key mappings) on our initial measurements, participants were required to complete one run with at least 80% correct discrimination of both the fixation and texture targets during this introductory session. All subjects met this performance benchmark in 2 to 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 five sessions by performing the practice version of the TDT in the upper left quadrant until they completed one run with at least 80% correct performance on both the fixation and texture tasks. This required no more than two



runs across all subjects and sessions. Aside from the drug/placebo administration that occurred on training days (details later), the experimental procedures for all training and testing sessions during phases A and B were identical.

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 the practice blocks. Because mean plasma concentration of donepezil peaks roughly 4 hours after oral ingestion of a 5-mg dose (Rogers & Friedhoff, 1998), subjects waited 3 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 left the laboratory and were instructed to try to have a full night's sleep that evening. They returned the following day (days 3 and 17) for the test sessions. After performing initial practice blocks in the upper left quadrant, participants were given a brief 5- to 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 still present in the subjects' bodies the day after drug administration. To ensure that any effects of donepezil administration were confined to the specified training and testing session pair, there was a 2-week interval (more than four times the 80-hour half-life) between phases A and B and between phase B and follow-up.

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 pharmacologic modulation. On this day, participants performed the full version of the TDT three times: once each in the untrained (upper right) and the two trained (lower left and lower right) quadrants. The order of these three runs was counterbalanced across subjects. Following completion of practice, participants were given a short rest before beginning the first run of the full TDT. Subjects were also required to take another 5- to 10-minute break before beginning testing on the next visual field quadrant.

Training was in the lower hemifield, whereas location-selectivity testing was in the upper hemifield. As the validity of this design rests on the assumption that TDT performance is symmetric across the horizontal meridian, we conducted a control experiment to test this assumption. This control experiment was designed

to replicate the main experiment without the training and pharmacology components. It was comprised of 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 exactly replicated the introductory and follow-up sessions from the main experiment (Figure 1B).

## 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 fit 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 bounds of 0–0.1). To control for improper fixation, only blocks for which fixation target discrimination performance 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 each fitted function and served as the performance measure for that 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), which included within-subject factors of session (training vs. testing vs. follow-up) and drug (donepezil vs. placebo) and between-subject factors of drug administration order (donepezil first vs. placebo first) and sex (women vs. men). Although not of primary interest here, sex differences in visual PL have been reported previously (Leclercq & Seitz, 2012; Leclercq, Hoffing, & Seitz, 2014; McDevitt et al., 2014).

## Results

### PL of texture discrimination is specific to the trained location

Visual PL of texture discrimination occurred as expected: the ISI needed to achieve threshold performance in the trained location decreased following each training session (Figure 3). For the trained location, the average ISI decrease between training and next-day testing sessions, collapsed across drug conditions, was  $23.4 \pm 4.6$  ms. From testing

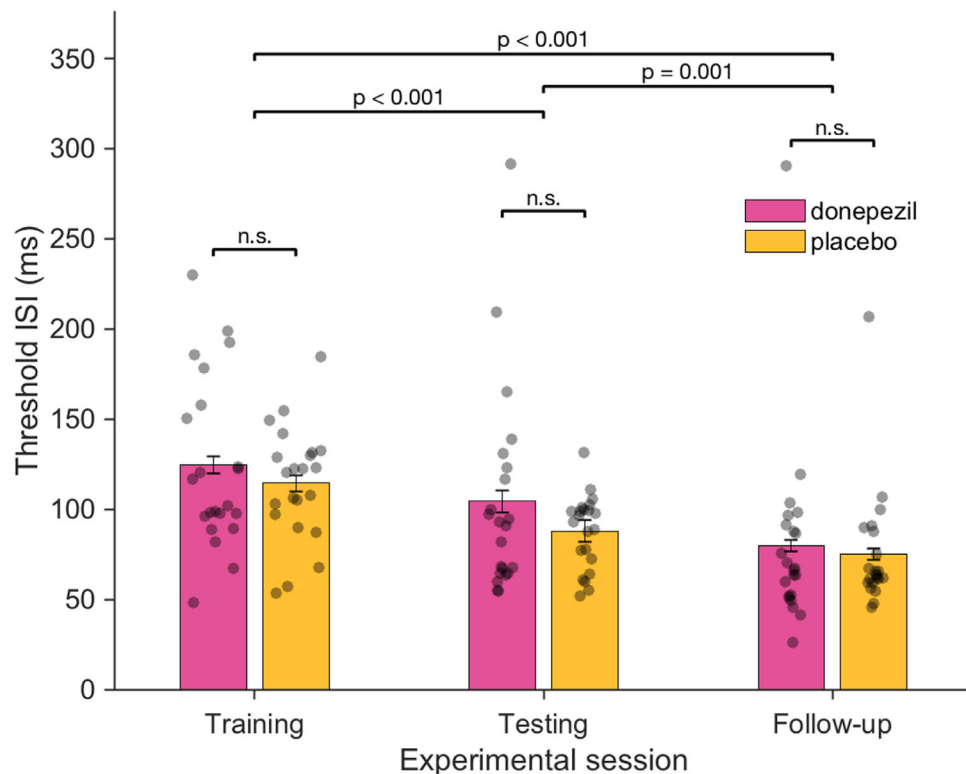


Figure 3. Transient cholinergic enhancement did not affect either task performance or the magnitude of PL for the trained conditions. Average threshold ISI durations for the donepezil and placebo conditions are plotted as a function of experimental session. PL occurred in both drug conditions, as average threshold ISI significantly decreased from training to testing to follow-up. Pairing a single dose of donepezil with training did not significantly boost these performance gains relative to placebo. Also, 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*. n.s. not significant.

to follow-up, ISIs again decreased an average of  $18.7 \pm 4.6$  ms at the trained location. Between training and the follow-up session 2 to 4 weeks later, the average threshold ISI duration at the trained location had decreased by  $42.1 \pm 6.3$  ms. A mixed-model ANOVA (Greenhouse-Geisser corrected) revealed a significant main effect of session,  $F(1.28, 23.03) = 14.97$ ,  $p = 3.54 \times 10^{-4}$ . Post-hoc comparisons employing paired samples *t*-tests and Bonferroni correction for multiple comparisons indicated that each pairwise difference was also statistically significant (Figure 3): training–testing ( $t = 4.51$ ,  $p = 5.76 \times 10^{-4}$ ), testing–follow-up ( $t = 4.25$ ,  $p = 0.001$ ), training–follow-up ( $t = 5.17$ ,  $p = 1.21 \times 10^{-4}$ ). There was not a significant interaction between the factors of session and sex,  $F(1.28, 23.03) = 2.00$ ,  $p = 0.169$ , indicating a lack of evidence for sex-dependent learning differences.

We assessed the location specificity of PL by comparing the average of each subject's performance at the two trained locations (one trained under donepezil and one under placebo) to his or her performance at the untrained location, all of which were measured during the follow-up session. The threshold ISI duration at the untrained location was  $23.7 \pm 6.3$  ms longer than the

threshold ISI at the trained locations, averaged over the donepezil and placebo conditions. A paired samples *t*-test indicated that 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 4A). This result is consistent with previous reports of location specificity of texture discrimination learning (Karni & Sagi, 1991; Mednick et al., 2003; Yotsumoto et al., 2008; Yotsumoto et al., 2009).

To test for possible sex differences in the location specificity of texture discrimination learning, we repeated these comparisons for female and male subjects separately. On average, threshold ISI duration in the trained location for female participants was  $22.1 \pm 8.8$  ms shorter than threshold ISIs in the untrained location. In the trained location in male participants, the average threshold ISI was  $26.4 \pm 8.6$  ms shorter than the average threshold ISI in the untrained location. This difference in the amount of location specificity of PL between the sexes was not significant, as indicated by an independent samples *t*-test,  $t(20) = 0.32$ ,  $p = 0.755$ . This finding is inconsistent with our previous report of significant sex differences in the location

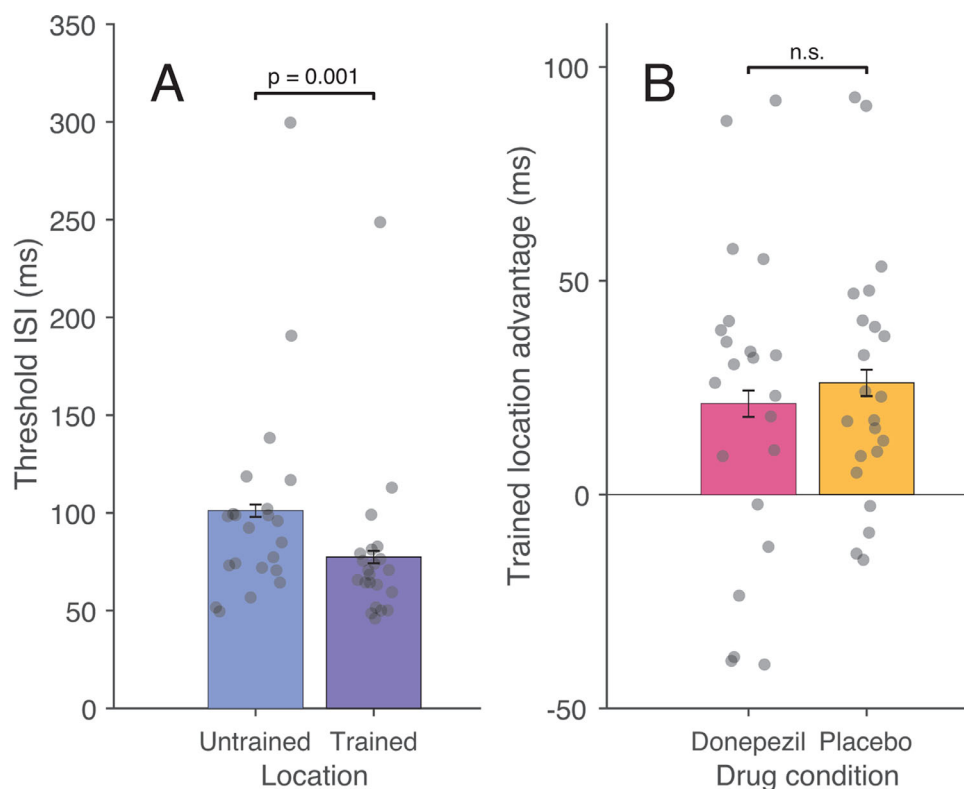


Figure 4. Location specificity of texture discrimination learning is not significantly affected by transient cholinergic enhancement. (A) Texture discrimination learning is specific to the trained location. Average threshold ISI durations are plotted as a function of visual field location. In the follow-up 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 significantly affect the location specificity of PL. The trained location advantage (difference in threshold ISI between the untrained and trained locations) at follow-up is plotted as a function of the drug administered during training. The average donepezil-trained location advantage was not significantly different from the placebo-trained location advantage. n.s. not significant.

specificity of PL of motion direction discrimination (McDevitt et al., 2014).

### Transient cholinergic enhancement did not significantly modulate texture discrimination ability

Rokem and Silver (2010) found that donepezil administration facilitated PL of motion direction discrimination but also significantly increased raw discrimination threshold values. To assess whether donepezil administration could have had a similar detrimental effect on texture discrimination ability, we compared participants' task performance under donepezil to that under placebo. For these comparisons only, we employed a reduced version of our mixed-model ANOVA that excluded data from the follow-up session, when no drug administration occurred.

On average, collapsed across the pharmacology-paired training and test sessions, threshold ISI durations in the donepezil condition were

$13.5 \pm 7.5$  ms longer than in the placebo condition. The reduced ANOVA showed that this difference, represented by the drug factor, was not significant,  $F(1, 18) = 0.35$ ,  $p = 0.560$ , suggesting that transient cholinergic enhancement neither impaired nor improved overall texture discrimination ability compared with placebo (Figure 3). The interaction between the drug and sex factors was also not significant in the reduced ANOVA,  $F(1, 18) = 0.18$ ,  $p = 0.675$ , providing no evidence for sex differences in cholinergic effects on TDT performance.

### Transient cholinergic enhancement did not significantly increase either the magnitude or the location specificity of texture discrimination learning

To test the impact of transient cholinergic enhancement on texture discrimination learning, we compared donepezil and placebo conditions for both task performance and training effects. The average

ISI reduction at the donepezil-trained location from training to testing was  $20.2 \pm 7.9$  ms. At follow-up, average ISI duration in the same quadrant had decreased by  $24.6 \pm 6.4$  ms since testing and by  $44.8 \pm 9.6$  ms since the training session. Between the training and testing sessions, the average threshold ISI in the placebo-trained quadrant was reduced by  $26.6 \pm 4.9$  ms, and it decreased an additional  $12.7 \pm 6.5$  ms between testing and follow-up. In the same location, the average ISI reduction was  $39.4 \pm 8.5$  ms between placebo training and follow-up. The interaction between the drug and session factors was not significant,  $F(1.76, 31.64) = 1.33$ ,  $p = 0.275$ , providing no evidence for our hypothesis that transient cholinergic enhancement would increase the magnitude of texture discrimination learning (Figure 3). Similarly, the lack of a significant three-way interaction among the ANOVA factors of drug, session, and sex,  $F(1.76, 31.64) = 0.33$ ,  $p = 0.691$ , offers no support for potential sex differences in cholinergic effects on PL of texture discrimination.

We also separately compared performance in the donepezil- and placebo-trained quadrants with corresponding performance levels in the untrained quadrant to explore cholinergic effects on the location specificity of PL. At follow-up, the average difference in threshold ISI was  $21.2 \pm 7.8$  ms between the untrained and donepezil-trained quadrants, and  $26.1 \pm 6.2$  ms between the untrained and placebo-trained quadrants. A paired samples *t*-test confirmed that this difference was not significant,  $t(21) = 0.79$ ,  $p = 0.438$ , consistent with no effect of transient cholinergic enhancement on the location specificity of texture discrimination learning (Figure 4B).

### No evidence for TDT performance asymmetries across the horizontal meridian

In our study, training occurred in the lower visual field (LVF), whereas testing performance in a novel location at the follow-up session was restricted to the upper visual field (UVF). This would pose a potential confound in our assessment of the location specificity of learning if TDT performance were asymmetric across the horizontal meridian. We are unaware of any evidence for such a performance asymmetry for the TDT. Nevertheless, differences between the LVF and UVF in potentially relevant factors, such as spatial resolution (Carrasco, Talgar, & Cameron, 2001; Talgar & Carrasco, 2002; Abrams, Nizam, & Carrasco, 2012; Silson et al., 2018), attentional modulation (Kristjánsson & Sigurdardóttir, 2008), crowding, (He, Cavanagh, & Intriligator, 1996; Fortenbaugh, Silver, & Robertson, 2015), and visual search (Previc & Naegele, 2001; Rezec & Dobkins, 2004), warrant further investigation of possible UVF/LVF performance asymmetries in texture discrimination.

We therefore conducted a second experiment in a group of naive subjects without any texture discrimination training. Specifically, we structured this control experiment so that it retained the structure of the main experiment but did not include 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 test whether the differences between the UVF and LVF observed at follow-up in the main experiment were indeed due to location specificity of PL and not to differences between UVF and LVF performance.

Average threshold ISIs were similar across the three quadrants measured at follow-up in the control experiment:  $129.4 \pm 18.3$  ms in the upper right,  $135.3 \pm 10.4$  ms in the lower left, and  $122.1 \pm 9.9$  ms in the lower right. A one-way repeated measures ANOVA revealed no significant 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 an inherent difference in texture discrimination performance between the LVF and UVF.

Finally, we examined the follow-up session data from both the main and control experiments as a function of experimental training and visual field location. Threshold ISIs from the lower left and lower right quadrants were averaged to generate a single LVF threshold for each participant. A two-way ANOVA with factors of experimental group (main vs. control) and hemifield (UVF vs. LVF) showed a significant main effect of group,  $F(1, 52) = 7.0$ ,  $p = 0.011$ ; presumably reflecting the performance benefits of texture discrimination training, but no significant effect of hemifield,  $F(1, 52) = 0.7$ ,  $p = 0.422$ . In addition, a paired samples *t*-test directly comparing untrained control subjects' performance between the two hemifields did not show a significant difference,  $t(5) = 0.04$ ,  $p = 0.971$ . Finally, there was a significant difference in performance between the UVF and LVF in the main subject group,  $t(21) = 3.75$ ,  $p = 0.001$ , consistent with the conclusion that this difference is because of the training that occurred in the LVF, and not a general performance asymmetry in texture discrimination (Figure 5).

## Discussion

We conducted a double-blind crossover study to examine the effects of transient cholinergic enhancement on PL of texture discrimination. Our training procedure resulted in a significant reduction in threshold ISI duration when paired with a single dose of either donepezil or placebo. However, the magnitude



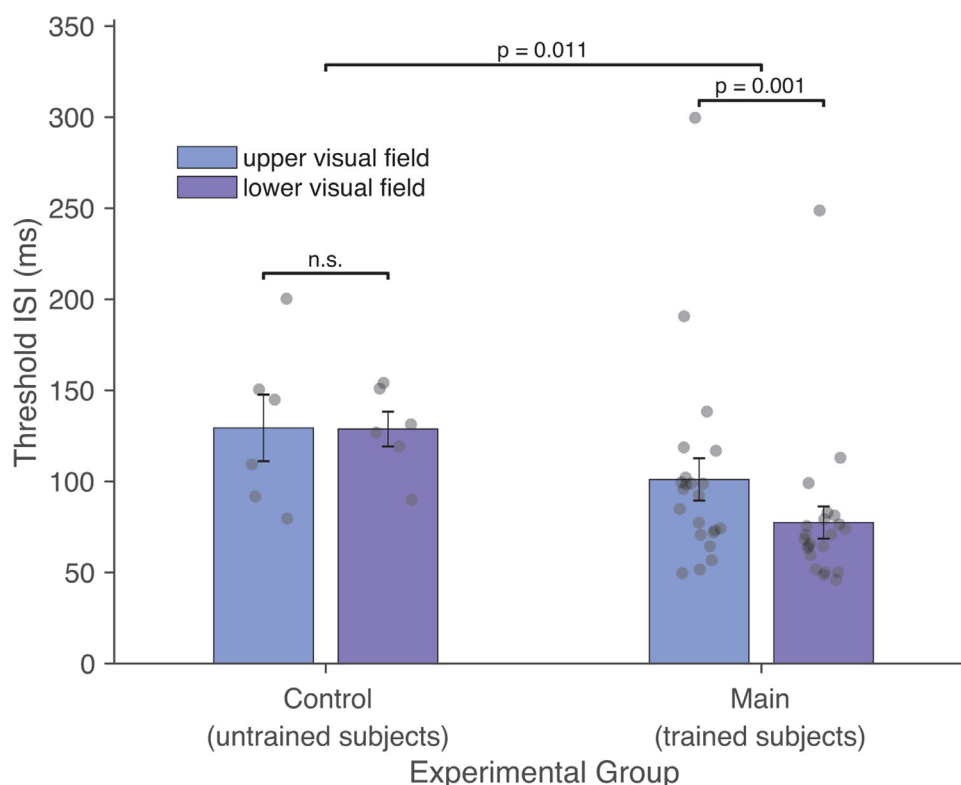


Figure 5. Texture discrimination is symmetric across the horizontal meridian. Average threshold ISI durations for the upper (UVF) and lower (LVF) hemifields are plotted as a function of experimental group. As expected, trained subjects' (main group) threshold ISIs were significantly shorter than those of untrained subjects (control group) in both locations. Similarly, trained subjects' performance in the trained location (LVF) was significantly better than their performance in the untrained location (UVF). However, in the untrained group, performance was not significantly different between the two hemifields. Circles depict individual data points; error bars represent *SEM*. n.s. not significant.

of texture discrimination learning was not significantly affected by transient cholinergic enhancement. We also compared task performance in the trained LVF quadrants and the untrained upper right quadrant and found that PL was location specific. However, like the magnitude of PL, the location selectivity of learning was not significantly affected by transient cholinergic enhancement. Finally, we conducted a control experiment and found that TDT performance was indistinguishable between the UVF and LVF in untrained subjects. This supports our interpretation that trained participants' superior performance in the lower (trained) versus upper (untrained) visual field was a consequence of training rather than an intrinsic performance asymmetry across the horizontal meridian.

### Cholinergic modulation of cortical plasticity and visual PL

The present study was partly motivated by considerable neurophysiological evidence that ACh

facilitates sensory cortical plasticity in a stimulus-specific fashion. Animal studies have shown that pairing electrical stimulation of the nucleus basalis—the chief source of cortical ACh—with stimulus presentation (a) amplifies stimulus-evoked cortical responses (Rasmusson & Dykes, 1988; Metherate & Ashe, 1993; Hars et al., 1993; Takata et al., 2011), (b) modifies the selectivity of neurons in sensory cortex (Metherate & Weinberger, 1990; Bakin & Weinberger, 1996; Froemke, Merzenich, & Schreiner, 2007), and (c) expands representations of the paired stimulus in cortical maps (Kilgard & Merzenich, 1998; Mercado et al., 2001). Direct application of ACh to sensory cortex reproduces these effects on responsiveness (Sillito & Kemp, 1983; Disney, Aoki, & Hawken, 2012), neuronal selectivity (Greuel, Luhmann, & Singer, 1988; Murphy & Sillito, 1991; Roberts et al., 2005), and plasticity of sensory cortical maps (Penschuck et al., 2002). These findings suggest that cholinergic transmission enhances sensory-evoked cortical responses, augmenting plasticity in the populations of neurons that represent these stimuli (see also Sarter et al., 2005; Rokem & Silver, 2010; Rokem & Silver, 2013; Kang, Huppé-Gourgues, & Vaucher, 2014).

Recent studies in human observers have described complex and variable effects of sustained cholinergic enhancement on visual PL. In these studies, a cholinesterase inhibitor was administered daily over several days. We previously reported that sustained cholinergic enhancement with donepezil increased the magnitude, rate, and specificity of motion direction discrimination learning compared with training under placebo (Rokem & Silver, 2010; Rokem & Silver, 2013). Another study (Chamoun et al., 2017) found that combining training on a three-dimensional multiobject tracking task with repeated donepezil administration resulted in significant learning effects in the donepezil group at an earlier stage in training compared with the placebo group.

Based on these reports of augmented PL following sustained cholinergic enhancement in healthy human subjects, Chung et al. (2017) conducted a pilot study to examine whether sustained cholinergic enhancement could increase the therapeutic effects of PL on amblyopic vision. Despite employing a letter identification training protocol that had previously elicited robust PL in observers with amblyopia (Chung et al., 2012), and a donepezil administration schedule that had been shown to increase the rate and magnitude of PL of motion direction discrimination in normally sighted observers (Rokem & Silver, 2010), Chung et al. (2017) found that sustained cholinergic enhancement decreased the rate of PL for single letter identification (at threshold contrast levels) and completely blocked learning of a crowded letter identification task that used high-contrast letters. More recently, multiple daily doses of donepezil were found to have no detectable effect on PL of single letter identification or crowded letter identification in the peripheral visual field of participants with normal vision (Levi et al., 2020).

These findings reveal that cholinergic effects on plasticity can be task-dependent: donepezil had different effects on PL of the same basic task (letter identification) in two different contexts (uncrowded and crowded letters) in the same observers (Chung et al., 2017). They also highlight that cholinergic effects on PL are not necessarily unidirectional: donepezil enhanced PL of motion-based visual tasks in normally sighted observers (Rokem & Silver, 2010; Rokem & Silver, 2013; Chamoun et al., 2017), impaired PL of letter identification tasks in observers with amblyopia (Chung et al., 2017), and had no observable effect on PL of letter identification (Levi et al., 2020) or texture discrimination PL (present study) in subjects with normal vision.

One intriguing possibility, consistent with the findings described earlier, is that cholinergic enhancement differentially modulates plasticity in the dorsal and ventral visual cortical processing streams (Ungerleider & Mishkin, 1982), with motion perception being associated mainly with the dorsal stream and

texture and letter perception with the ventral stream. Specifically, cholinergic enhancement may facilitate PL when the training task is more associated with dorsal than ventral visual cortical stream processing. The emergence of dorsoventral differences in cholinergic receptor density as early in the processing hierarchy as cortical area V2 (Eickhoff et al., 2008) provides a functional substrate that may account for the apparent discrepancies in the literature on ACh and visual PL.

## Potential mechanisms underlying cholinergic facilitation of learning

Because donepezil was administered throughout both training and testing in the studies discussed earlier, it is unclear which stage(s) of learning were impacted by increased ACh signaling: stimulus processing during training (encoding), offline stabilization that occurs during both wake and sleep (consolidation), and/or retrieval.

Beer et al. (2013) approached this problem by using a single dose of nicotine, a rapidly metabolized nicotinic ACh receptor agonist, to isolate the effects of transient cholinergic enhancement on PL consolidation. After a single session of texture discrimination training, but prior to testing, subjects received either nicotine-rich chewing tobacco or an inactive control substance. The drug group showed greater texture discrimination learning but no significant change in the specificity of learning, suggesting that nicotine increased the magnitude of texture discrimination PL 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, Duggan, & Mednick, 2015), as cortical ACh release peaks during REM sleep (Jasper & Tessier, 1971; Marrosu et al., 1995).

The increased magnitude of texture discrimination learning following nicotine administration 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 PL. However, there are a number of differences between our study and that of Beer et al. (2013), including drug (donepezil vs. nicotine), timing of drug administration (prior to training vs. after training), sex composition of the subjects (mixed sex vs. all men), performance metric (threshold ISI vs. percent correct responses), and spatial arrangement of targets (discrimination of a single target vs. comparison of two targets in opposing quadrants).

Additionally, our TDT task implemented variable ISIs within each session through the method of descending limits, whereas texture discrimination training in Beer et al. (2013) employed a fixed

ISI. Previous work investigating the dynamics of consolidation of PL has shown that the latter training method induces less sensory adaptation and enhances texture discrimination learning, compared with the former (Harris & Sagi, 2015; Censor, Harris, & Sagi, 2016).

Moreover, the method of descending limits that we employed results in more difficult trials being concentrated near the end of the training session, whereas the fixed ISI procedure used by Beer et al. (2013) results in a more constant task difficulty throughout the session. It is therefore possible that these differences in training procedures may also account for the divergent findings of the two studies. We also note that the method of descending limits that we have employed is the most commonly used training procedure in studies of PL of texture discrimination (Karni & Sagi, 1991; Karni & Sagi, 1993; Karni et al., 1994; Gais et al., 2000; Schwartz et al., 2002; Mednick et al., 2003; Yotsumoto et al., 2008). Further research is needed to determine the conditions under which increased ACh receptor signaling facilitates PL and cortical plasticity.

Although 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 training. 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). In our study, we administered donepezil 3 hours prior to the onset of training so that increased cholinergic signaling would peak during encoding. However, because donepezil's half-life is approximately 80 hours (Rogers & Friedhoff, 1998), ACh levels were also elevated during consolidation and retrieval in our study. Despite this, we did not find any significant effects of transient cholinergic enhancement on PL of texture discrimination.

Could it therefore be the case that stimulus encoding during PL of texture discrimination was unaffected by cholinergic enhancement in our study? The evidence presented earlier for facilitation of sensory processing 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). Physiology studies in animal models, in which ACh can be directly applied to neurons in sensory cortex, offer strong support for this theory. In macaque primary visual cortex, application of cholinergic agonists enhances feedforward thalamocortical transmission and simultaneously inhibits intracortical signaling (Disney,

Aoki, & Hawken, 2007; Disney et al., 2012). Excitatory receptive field size is reduced by ACh application to marmoset visual cortical neurons (Roberts et al., 2005), consistent with increased weighting of thalamocortical inputs from the lateral geniculate nucleus that have small receptive fields. Similarly, donepezil administration in humans reduces the spatial extent of excitatory stimulus-evoked functional magnetic resonance imaging responses in early visual cortex (Silver, Shenhav, & D'Esposito, 2008) and enhances perceptual spatial resolution (Kosovicheva et al., 2012; Gratton et al., 2017).

Thus cholinergic enhancement biases cortical circuit dynamics toward feedforward processing of extrinsic stimuli and could therefore be especially beneficial for encoding high spatial resolution information. Although we did not observe an effect of cholinergic enhancement on PL of texture discrimination in the present study, this could be because performance was not limited by the spatial resolution of perception in this task. This would be consistent with the finding 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 (Wang, Cong, & Yu, 2013).

## No evidence for an asymmetry in TDT performance between the UVF and LVF

A number of perceptual asymmetries across the horizontal meridian are known to exist. For example, higher spatial resolution of perception in the LVF vs. UVF at equivalent eccentricities likely contributes to the LVF performance advantage for tasks that require fine-grained spatial segmentation of visual information (Carrasco et al., 2001; Talgar & Carrasco, 2002; Abrams et al., 2012). Regarding potential UVF/LVF asymmetries in TDT performance specifically, Pourtois et al. (2008) reported significant changes in performance and electroencephalogram activity following training in the UVF but detected no such changes in a second group that trained in the LVF. However, the present study and others (Karni & Sagi, 1991; Mednick et al., 2003; Yotsumoto et al., 2009; McDevitt et al., 2015) have convincingly demonstrated texture discrimination learning in the LVF. Results from our control experiment suggest that the location selectivity of training effects in the main experiment is in fact because of the spatial specificity of PL itself, and not to an inherent asymmetry in TDT performance between the upper (untrained) and lower (trained) visual fields.

## Study limitations

It is also possible that design limitations could have played a role in our null results. Participants varied in

factors that are known to influence pharmacokinetics (e.g., body weight), yet each subject received the same 5-mg dose of donepezil in our study, and we did not directly assess the effectiveness of donepezil in our participants. However, we (Silver et al., 2008; Rokem et al., 2010; Kosovicheva et al., 2012; Gratton et al., 2017) and others (Zaninotto et al., 2009; Boucart et al., 2015) have documented reliable effects of this dose of donepezil on cortical responses and behavioral performance in previous studies. In any case, it is possible that individual differences in donepezil absorption and metabolism reduced sensitivity for detecting effects of transient cholinergic enhancement on PL.

Alternatively, the scope of cholinergic enhancement induced by a single low dose of donepezil may be 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 dose of donepezil reduced perceptual eye dominance plasticity that was triggered by a few hours of monocular deprivation (Sheynin et al., 2019) argues against this. Overall, although there are multiple reports of a facilitatory effect of cholinergic enhancement on visual cortical plasticity in humans, it is less clear that the dose-response relationship is monotonic. One possibility is that this function has an inverted-U shape, as has been described for the multifaceted relationship between dopamine and cognitive control (Cools & D'Esposito, 2011). Such a relationship for ACh may help account for the variability of cholinergic effects reported in the literature, and it is largely supported by the relevant human neuroimaging literature (Bentley, Driver, & Dolan, 2011).

## Conclusions

We found robust location-specific PL of texture discrimination with training. Acute administration of a single dose of donepezil prior to training did not significantly affect the magnitude or the location specificity of texture discrimination learning, compared with placebo. However, it is important to note that employing a more prolonged period of drug administration and/or a higher dose could result in cholinergic effects on PL of texture discrimination. In a control experiment, we demonstrated that TDT performance is symmetric across the horizontal meridian, thereby providing evidence against the possibility that the location specificity of PL that we observed in our main experiment was attributable to an LVF performance advantage. There are several possible explanations that could account for the absence of a significant cholinergic effect in our study compared with previous ones, including (a) differential modulation of

ventral and dorsal visual cortical stream plasticity by cholinergic enhancement; (b) different pharmacologic effects of the cholinesterase inhibitor donepezil and the receptor agonist nicotine; and (c) different effects of single versus multiple doses of donepezil. Future studies should employ a combination of pharmacologic tools and PL to continue developing our understanding of and ability to meaningfully leverage plasticity in the human brain.

*Keywords:* acetylcholine, perceptual learning, plasticity, texture discrimination task, visual field asymmetry

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