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Spatial Resolution in Perception and Working Memory

By

Adeola Natasha Harewood Smith

A dissertation submitted in partial satisfaction of the

requirements for the degree of

Doctor of Philosophy

in

Vision Science

in the

Graduate Division

of the

University of California, Berkeley

Committee in charge:

Professor Michael Silver, Chair

Professor Lynn Robertson

Professor Stephen Palmer

Fall 2017

Abstract

Spatial resolution in perception and working memory

by

Adeola Natasha Harewood Smith

Doctor of Philosophy in Vision Science

University of California, Berkeley

Professor Michael Silver, Chair

The ability to discriminate individual items in the presence of flankers is necessary for tasks such as reading and driving. The reduction in the ability to identify an item in peripheral vision due to the presence of flankers is called crowding. Crowding tasks provide a measure of the spatial resolution of visual perception. Previous studies have found better performance on crowding tasks in the lower visual field than in the upper visual field, and this effect is known as the lower visual field advantage. However, when the size of the upper and lower visual field extent are taken into account by placing stimuli at locations with the same percentage of visual field extent, the lower visual field advantage goes away.

Spatial working memory (SWM) is the short-term storage of locations of items not currently visible in the environment for immediate use. Manipulation of cholinergic or dopaminergic signaling alters the spatial tuning of macaque prefrontal cortical neurons during the delay period of a SWM task and can improve SWM performance in primates. Moreover, increasing synaptic levels of acetylcholine reduces the excitatory receptive field size of neurons in marmoset primary visual cortex and sharpens the spatial tuning of visual cortical fMRI responses in humans. These results point to cholinergic enhancement leading to increased spatial resolution and cholinergic and dopaminergic enhancement improving spatial working memory.

In chapter one of this dissertation, I discuss the relationship between crowding and visual field shape. I show that for radially configured flankers there is a lower visual field advantage for critical spacing (the minimum distance between a target and its flankers that is required for a certain level of performance on a crowding task) when crowded stimuli are placed at the same eccentricity. This suggests that the spatial resolution of perception is better in the lower visual field than in the upper visual field. When stimulus locations are matched for the same percentage of visual field extent, however the lower visual field advantage for critical spacing is no longer present. We did not observe a lower visual field advantage for stimuli with a tangential configuration.

In chapter two I present a study that examined the effects of cholinergic and dopaminergic enhancement on spatial working memory. I found that pharmacological enhancement of the cholinergic system (using donepezil) and the dopaminergic system (using levodopa/carbidopa) did not result in improved spatial working memory precision, which we

defined as subjects being able to notice smaller changes in the spatial location of a remembered stimulus.

The first study demonstrates that spatial resolution is different in the lower and upper visual field when stimuli are oriented radially. The second study concludes that the precision of spatial resolution in working memory is not limited by the spatial resolution of perception and that cholinergic or dopaminergic enhancement through an acute dose of donepezil or levodopa/carbidopa, respectively, does not improve spatial resolution in working memory.

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Introduction

Spatial vision includes the study of perception of visual space and how the visual system processes and maintains information about space, spatial locations, and spatial relationships. Previous studies have shown that perceptual anisotropies exist throughout the visual field. For example, performing an acuity task at the fovea will result in better performance than executing the same acuity task in the periphery (Low, 1951). Another visual field anisotropy exists between the upper and lower visual field, especially when spatial attention is involved (He et al., 1996). This is called the lower visual field advantage. He et al. (1996) showed that a lower visual field advantage exists in crowding, with less crowding in the lower visual field than in the upper visual field. A follow-up study completed by Fortenbaugh et al. (2015) found that this lower visual field advantage is largely due to the fact that the lower visual field is bigger than the upper visual field. Specifically, matching stimulus locations for the same percentage of visual field extent eliminates the lower visual field advantage in crowding. They also found that the lower visual field advantage is dependent on endogenous spatial attention.

Previous work by He et al. (1996) proposes that the lower visual field has better attentional resolution compared to the upper visual field and that this is responsible for the lower visual field advantage. The observed lower visual field advantage for tasks requiring spatial attention, such as visual search, motion tracking (He et al., 1996), and crowding (He et al., 1996; Fortenbaugh et al. 2015) supports the proposal by He et al (1996) that attentional resolution is better in the lower visual field than in the upper visual field.

Acetylcholine and dopamine are neurotransmitters that have been shown to play multiple roles in cognition and perception. Cholinergic enhancement increases the spatial resolution of visual representations by reducing the excitatory receptive field size of marmoset V1 neurons (Roberts et al., 2005) and decreasing the spatial spread of excitatory fMRI responses to visual stimulation in human early visual cortex (Silver et al., 2008). Local administration of dopaminergic drugs that target D1 dopamine receptors sharpen the spatial tuning of delay period activity in D1 prefrontal cortex neurons in macaque monkeys performing a SWM task (Williams and Goldman-Rakic, 1995; Vijayraghavan et al., 2007).

Spatial working memory is a mechanism that allows for information concerning the locations and spatial configurations of visual stimuli to be held for immediate use and has been studied using a variety of tasks. Some of these have used a change detection paradigm similar to that used in other visual working memory tasks (Luck and Vogel, 2013). Others have used a delay estimation task and asked subjects to move the changed stimulus to the encoded location (Pearson et al., 2014) or have presented a single object and asked subjects to determine how far the stimulus had been displaced from its original location by moving the test stimulus to the same location of the stimulus in the original memory array (Awh & Jonides, 2001).

In this dissertation, I will describe our research to understand how individual differences and neurochemical factors affect different aspects of spatial vision. The first study examines the relationships among visual field shape, critical spacing, and spatial attention. The second study delves into the neurochemistry of spatial working memory precision.

Chapter 2

The lower visual field advantage in critical spacing in visual crowding is accounted for by visual field shape

2.1 Abstract

Performance is better in the lower, compared to the upper, visual field for a variety of visual tasks, including crowding. Recently, Fortenbaugh et al. (2015) showed that the lower visual field advantage in orientation discrimination of crowded gratings centered at the vertical meridian could be accounted for by an asymmetry in the shape of the visual field. Specifically, individuals with a larger difference between the size of their upper and lower visual fields have a greater lower visual field advantage in a crowding task, and this correlation between visual field shape and performance asymmetry depends on subjects directing endogenous spatial attention to the stimulus location. Here, we extend these findings by studying visual field asymmetries in critical spacing, defined as the minimum distance between a target and its flankers that enables a certain level of performance on a crowding task. First, we measured upper and lower visual field extents in each participant using a Goldmann perimeter. Participants then completed a crowding task that required them to discriminate the orientation of a target grating in the presence of flankers arranged in either a tangential or radial configuration. We found that when flankers were arranged radially and stimuli were placed at the same eccentricity in units of degrees of visual angle, critical spacing was smaller in the lower visual field compared to the upper visual field, consistent with a lower visual field advantage. However, no lower visual field advantage in critical spacing was observed when stimulus locations were matched based on percentage of visual field extent. We did not observe a lower visual field advantage when the flankers were arranged tangentially. Finally, we manipulated endogenous spatial attention by varying the amount of uncertainty that subjects had about possible stimulus locations (the stimulus could appear in one of two locations, instead of appearing in the same location on every trial throughout a block) and did not find any detectable effect of spatial attention on critical spacing in the tangential condition. We did however find a significant effect of spatial attention on critical spacing in the radial condition.

2.2 Introduction

Visual perception is anisotropic across the visual field for many tasks. For example, performance on an acuity task is better at fixation compared to the periphery (Kerr, 1971; DeValois & DeValois, 1988). Additionally, high spatial frequency stimuli are processed more efficiently in the right visual field, and low spatial frequency stimuli are processed more efficiently in the left visual field (Kitterle, Hellige, & Christman, 1992; Kitterle & Selig, 1991; Ivry & Robertson, 1998). Performance on certain tasks is better in the lower than in the upper visual field, a phenomenon known as the lower visual field advantage. This lower visual field advantage has been demonstrated for visual acuity (Skrandies, 1987), perception of illusory contours (Rubin, Nakayama, & Shapley, 1996), and target detection and discrimination (Abrams et al., 2012; Carrasco et al., 2004; Carrasco et al., 2001).

Here, we employed a visual crowding task to assess whether a lower visual field advantage exists for critical spacing. Crowding is a phenomenon in which identification of a stimulus in the periphery is difficult due to surrounding stimuli or flankers. Critical spacing is the minimum target/flanker distance required to enable a certain level of performance on a crowding task. It has been proposed that the lower visual field advantage is due to better attention resolution in the lower visual field than in the upper visual field (He et al., 1997). This proposal is based on the fact that performance is better in the lower, compared to the upper, visual field on tasks requiring attention such as visual search and motion tracking (He et al., 1996). Although orientation discrimination of a central grating flanked by gratings at a fixed target/flanker distance has been shown to exhibit a lower visual field advantage (He et al., 1996; Fortenbaugh et al., 2015), it is currently unknown whether a lower visual field advantage exists for critical spacing.

Interestingly, the shape of the visual field (defined as the set of locations for which visual stimuli can be perceived when the eye is directed forward) is asymmetric. Specifically, the upper visual field extent is typically smaller than the lower visual field extent (Niederhausen & Mojon, 2002). Moreover, individual visual field shapes differ across individuals, especially near the vertical meridian, due to physical differences in the features of individual faces, including the brow and cheekbones.

In many studies of visual perception, stimuli are placed at eccentricities (in units of degrees of visual angle defined in a polar coordinate system) without much consideration of visual field asymmetries. Recently, Fortenbaugh et al. (2015) used a modified version of the He et al. (1996) crowded orientation discrimination task to assess the relationships among individual differences in visual field shape, spatial attention, and crowding. They found that performance on this crowding task was similar for stimuli that were placed at locations along the upper and lower vertical meridians at equal percentages of visual field extent. Thus, the asymmetry between the upper and lower visual field extents accounted for the lower visual field advantage, as assessed by percentage correct performance on a crowding task with a fixed target/flanker grating distance.

In addition, Fortenbaugh et al. (2015) found that the upper/lower visual field performance ratio for crowding correlated with the ratio of upper and lower visual field extents across participants only when endogenous spatial attention was focused on the crowded target. In contrast, distributing spatial attention across two possible target locations eliminated the correlation between performance ratios and visual field ratios across subjects, but a clear lower visual field advantage remained.

It is well known that attention can facilitate visual perception (Carrasco, 2011), and attention usually improves performance on crowding tasks (Yeshurun & Rashal, 2010; Fortenbaugh et al., 2015). However, there are conflicting results in the literature regarding whether attention affects critical spacing, a measure of the spatial resolution of perception. Scolari et al. (2007) found no significant effect of attentional pre-cueing on critical spacing, but they did observe that attention significantly improved the accuracy of target discrimination. Nazir (1992) also found that pre-cueing did not have a significant effect on critical spacing (or “gap resolution”), while another study reported that directing attention with a pre-cue decreased critical spacing (Yeshurun & Rashal, 2010). Studies utilizing color pop-out revealed reduced crowding and critical spacing when the target was a different color or surrounded by a different color than that of the distractors or flankers (Poder 2007; Scolari et al., 2007).

In the present study, we tested whether critical spacing in visual crowding exhibits a lower visual field advantage for both tangential and radial flankers. We also examined the roles of individual differences in visual field shape and endogenous spatial attention on critical spacing.

2.3 Methods

2.3a Participants

The Committee for the Protection of Human Subjects at the University of California, Berkeley, approved all experimental procedures, and all participants provided written informed consent in accordance with the Declaration of Helsinki before the study began. All participants reported 20/20 visual acuity, either without optical correction or with optical correction by contact lenses. Exclusion criteria included wearing eyeglasses (as these can restrict the visual field; Steel et al., 1996) and eye and neurological diseases of any kind. Twenty-six subjects participated in the tangential experiment (6 males, 20 females) and 28 subjects participated in the radial experiment (7 males, 21 females). On average subjects were 25.04 years old (range: 20-46) in the tangential study and 22.13 years old (range: 18-31) in the radial study.

2.3b Visual Field Measurement

A Goldman Kinetic Perimeter was used to measure upper and lower visual field extent (VFE) along the vertical meridian in each participant. The subject placed his or her head in the half-dome and fixated on its center. The experimenter then moved a III4e test target light (0.44 degree test spot at a viewing distance of 30 cm; target luminance of 318 cd/m² on a background luminance of 10 cd/m²) from the periphery towards fixation. The subject maintained fixation at the center of the dome and pressed a button when he or she saw the target light first appear in the periphery. A small telescope on the perimeter allowed the experimenter to verify that fixation had been maintained. Trials for which fixation had not been maintained were discarded. Each subject performed one practice trial each for the upper and lower visual fields. Three or four measurements were collected in random order for each vertical meridian and were rounded to the nearest degree. The visual field extent for the upper and lower visual fields in each participant was defined as the average of these trials.

2.3c Orientation discrimination tasks: General methods

Testing was conducted in a light attenuated room. Visual stimuli were presented on a NEC Multisync FE992 CRT monitor with a refresh rate of 75 Hz using PsychoPy software (Peirce, 2009). Subjects viewed the monitor at a distance of 30 cm, and a chin and forehead rest stabilized head position.

The experimenter monitored eye fixation using an infrared camera. On each trial, the experimenter assessed whether or not an eye movement was made during the trial. If an eye movement was made, the subject was informed of this by presentation of an auditory tone, and

that trial was removed from further analysis. Next, a different tone indicated that the subsequent trial would begin in 150 ms. Two types of orientation discrimination tasks were used: the single grating task and the crowded (three gratings) task.

2.3d Single grating orientation discrimination task

For the radial experiment, subjects completed a single-grating task to enable presentation of gratings in the subsequent crowding task with a size and spatial frequency that was a fixed proportion above the single grating orientation discrimination threshold for each participant. The screen resolution was 1600 x 1200 pixels. Each trial began with presentation of a 1-degree black fixation cross for 500 ms, followed by presentation of a single sinusoidal grating (100% contrast) for 150 ms centered on either the upper or lower vertical meridian at 8 degrees eccentricity. The orientation of the grating was either 45 degrees (tilted right from vertical) or 135 degrees (tilted left), and the subject pressed either the left or right arrow key on a keyboard to indicate the direction of tilt.

The size and spatial frequency of the grating changed according to a 1-up / 3-down staircase. Specifically, three correct responses in a row resulted in a decrease in grating size, and each incorrect response resulted in an increase in grating size. The spatial frequency varied as a function of grating size such that there were always 4 luminance cycles across the circular aperture. The starting size was 0.65 degrees of visual angle, and the step size for the staircase was 0.065 degrees of visual angle.

Stimuli were presented at only one location (upper or lower) in each run, and each run contained 120 trials. We calculated the threshold for 79% correct orientation discrimination using the Palamedes Toolbox for Matlab (Prins & Kingdom, 2009). Alpha (threshold), beta (slope of the psychometric function), and lambda (lapse rate) were free parameters, and values of lambda were bounded between 0 and 1.

2.3e Crowding task

The stimuli were three circular gratings with a contrast of 100%. For the tangential experiment (26 subjects), the grating diameter was always 1.5 degrees of visual angle, and the spatial frequency was always 2.5 cycles per degree. For the radial experiment (28 subjects), the grating size was 50% greater than the threshold grating size obtained from the single grating task for each participant, and the spatial frequency varied as a function of grating size so that there were always 4 luminance cycles across the circular aperture.

For the tangential experiment, the screen resolution was 1280 by 1024 pixels, and for the radial study, it was 1600 by 1200 pixels. As in Fortenbaugh et al. (2015), gratings were presented at one of four target locations on each trial. The central grating was placed in the upper visual field (12 degrees for tangential / 8 degrees for radial), the lower visual field (12 degrees for tangential / 8 degrees for radial), matched upper % visual field extent (VFE), or matched lower %VFE (Figure 2.1). For matched lower %VFE trials, the location corresponding to (12 degrees tangential / 8 degrees radial) in the upper visual field was converted to %VFE for each participant, and stimuli were presented at the same %VFE in the lower visual field. For matched upper %VFE trials, the location at (12 degrees tangential / 8 degrees radial) in the lower visual

field was converted to % VFE, and stimuli were presented at this %VFE value in the upper visual field (Figure 2.1).

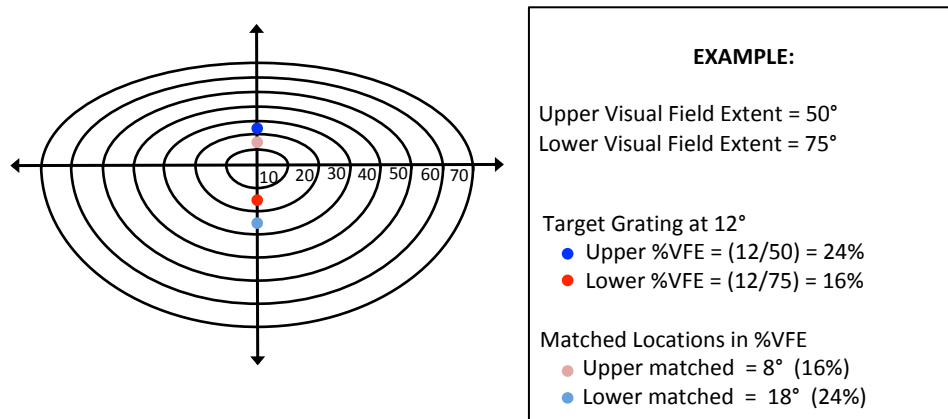


Figure 2.1 | Critical spacing was measured for pairs of locations in the upper and lower visual field that either had the same eccentricity or the same percentage of visual field extent. In this example, the eccentricity of the blue points is 24% of the visual field extent (VFE), but the points have different eccentricities in degrees of visual angle (12 degrees in upper visual field and 18 degrees in lower visual field). Similarly, the red point is at 12 degrees of visual angle (16% VFE), and its matching pink point with the same % VFE in the upper visual field is at 8 degrees of visual angle.

Each trial began with presentation of the fixation cross for 500 ms, followed by presentation of three gratings, arranged tangentially or radially, for 150 ms. The orientation of each grating was either 45 degrees (tilted right from vertical) or 135 degrees (tilted left) and was randomly assigned for each grating, resulting in eight possible combinations of target and flanker orientations. The subject then pressed either the left or right arrow key on a keyboard to indicate the direction of tilt of the center (target) grating.

The target/flanker distance was adaptively adjusted using a 1-up / 3-down staircase that converged to 79% correct. Specifically, three correct responses in a row resulted in a decrease in target/flanker distance, and each incorrect response resulted in an increase in target/flanker distance. In the tangential experiment, the starting target/flanker distance on each run was 4 degrees center-to-center, with a staircase step size of 0.2 degrees for the first four reversals and 0.05 degrees for the remainder of the run. For the radial experiment, the starting target/flanker distance on each run was 3 degrees center-to-center, with a staircase step size of 0.3 degrees. Each run contained 120 trials.

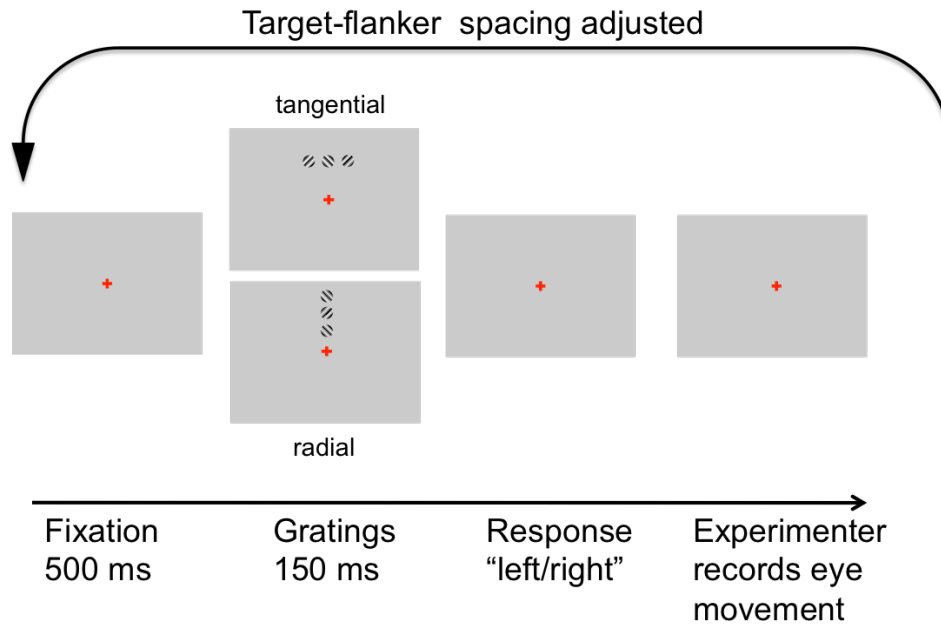


Figure 2.2 | Schematic of the trial sequence for the crowding task. Subjects reported the direction of tilt of the center grating. Both tangential and radial configurations are shown, but only one of these configurations was used for each experimental session.

The crowding task for both the tangential and radial studies consisted of two attention conditions: focused and divided. In the focused attention condition, stimulus location was blocked, so subjects knew before the onset of each trial where the target and flankers would be presented. In the divided attention condition, stimuli could appear in either the upper or the lower visual field with equal probability on each trial.

Critical spacing was defined as the center-to-center target/flanker distance corresponding to 79% correct, calculated using the Palamedes Toolbox for Matlab (Prins & Kingdom 2009). The model parameters were alpha, beta, and lambda, and values of lambda were bounded between 0 and 1. We excluded runs for which the goodness of fit (root-mean-squared error) of the psychometric curve was more than two standard deviations from the mean across subjects, or for which the lapse rate was more than 21% (100% - performance threshold of 79%). Based on these criteria, the following data were excluded from the tangential experiment: five runs from the focused upper VF condition, five from divided upper VF, two from focused lower VF, three from divided lower VF, one from divided upper matched, four from focused lower matched, and five from divided lower matched. For the radial experiment, all the data from one subject were excluded because we were unable to fit a psychometric curve to data for any condition. Additionally, based on the previously stated criteria, the following data were excluded from the radial experiment: six runs from the focused upper VF condition, fourteen from divided upper VF, one from focused lower VF, eight from divided lower VF, six from focused upper

matched, nine from focused lower matched, eight from divided upper matched, and twelve from divided lower matched.

2.4 Results

2.4a Tangential Experiment

Subjects performed an orientation discrimination task (Figure 2.2) on the center grating of a set of three gratings arranged in a tangential (horizontal) configuration. The eccentricity of the gratings along the vertical meridian was 12 degrees in the upper VF, 12 degrees in the lower VF, a location in the lower VF that had a % visual field extent (VFE) that matched that of the 12-degree upper VF for that participant, and a location in the upper VF that had the same % VFE as the 12-degree lower VF stimulus (Figure 2.1).

There were two attention conditions: focused attention, in which the stimulus location was fixed throughout the run, and divided attention, in which the stimulus could appear in either the upper or lower visual field on each trial. To analyze the data, we employed a linear mixed-effects model using the lmerTest package (Kuznetsova et al., 2017) in the R programming language and software environment (R Development Core Team, 2008).

Critical spacing was modeled as a function of the fixed effects of visual field (upper vs. lower), attention (focused vs. divided), matching (degrees of visual angle vs. percentage of visual field), and the interaction among all three factors. Subject was defined as a random-effects factor to account for between-subject variability and visual field and attention were set as random slopes. Estimates of the effect (β) and the standard error of the model coefficient (SE) are reported. We found no main effect of visual field ($\beta = .102^\circ$, $SE = .087^\circ$, $p = .25$), matching ($\beta = .002^\circ$, $SE = .060^\circ$, $p = .97$), or attention ($\beta = .063^\circ$, $SE = .059^\circ$, $p = .293$). In addition, there were no significant interactions between visual field and attention ($\beta = 0.090^\circ$, $SE = .059^\circ$, $p = .12$), attention and matching ($\beta = -.047^\circ$, $SE = .059^\circ$, $p = .42$), nor was there a three-way interaction of attention, visual field, and matching ($\beta = -.015^\circ$, $SE = .059^\circ$, $p = .79$). However, we found a significant interaction between visual field and matching ($\beta = .351^\circ$, $SE = .059^\circ$, $p < .001$), which we explored with paired t-tests.

Because there was no significant effect of attention, we combined the data in the focused and divided attention conditions for further analysis. In the combined data, critical spacing in the lower visual field was not significantly different than critical spacing in the upper visual field ($t(21) = 1.63$, $p = .12$) (Figure 2.3, Figure 2.4). And when stimuli were presented at the same percentage of visual field extent, there was no significant difference between the upper visual field and the lower matched %VFE ($t(18) = -1.54$, $p = .14$), or between the lower visual field and the upper matched %VFE ($t(25) = -0.93$, $p = .35$). These results are not consistent with previous findings that there is a lower visual field advantage (He et al., 1996; Fortenbaugh et al., 2015).

It is possible we did not observe a significant lower visual field advantage because we measured critical spacing at a distance closer to fixation than previous studies, which measured percent correct at 20 degrees eccentricity (He et al., 1996; Fortenbaugh et al., 2015).

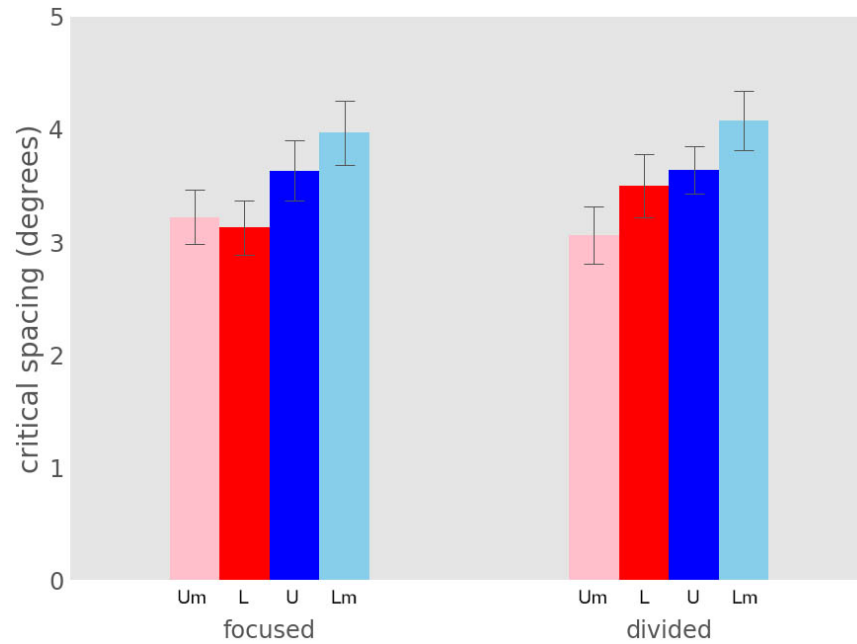


Figure 2.3 | Critical spacing for tangential configuration. Upper(U),lower (L), upper matched (Um), and lower matched (Lm) critical spacing averages all plotted for both focused and divided attention conditions. Error bars are between-subject standard errors of the mean.

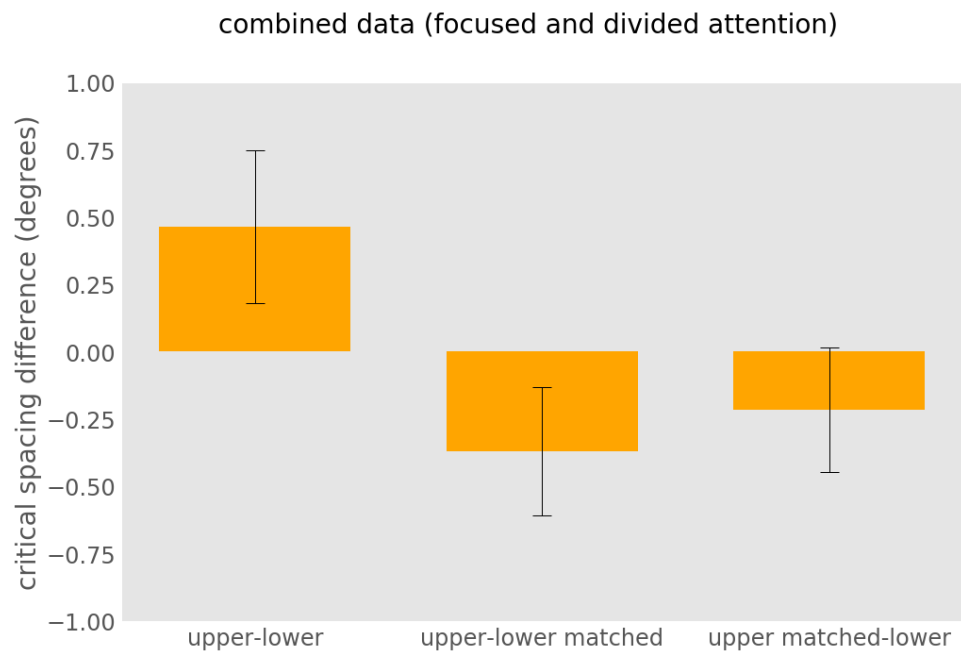


Figure 2.4 | Differences in critical spacing (combined attention conditions). The difference between critical spacing in the upper and lower conditions, upper and lower matched conditions, and between the upper matched and lower conditions were not significantly different from zero. Error bars are within-subject standard errors of the mean.

2.4b Radial Experiment

Previous research has suggested fundamental differences in crowding for stimuli in tangential versus radial configurations (Toet & Levi, 1992). Specifically, critical spacing is smaller for stimuli in tangential compared to radial arrangements. We therefore repeated the tangential experiments described above for a set of three gratings with a radial configuration. In this experiment, we customized the grating size for each subject based on orientation discrimination performance for a single grating (see Methods and Toet & Levi (1992)). On average, the threshold grating size was significantly greater in the upper (0.46 degrees of visual angle) compared to the lower (0.41 degrees) visual field ($t(27)=3.17$, $p=.003$). This result is consistent with visual acuity being better in the lower visual field than in the upper visual field (Skrandies, 1987). For each subject we averaged the upper and lower visual field thresholds for the single-grating task and used a grating size 50% larger than this average for the three-grating crowding experiment. As in the tangential condition, we employed a linear mixed-effects model using the lmerTest package (Kuznetsova et al., 2017) in the R programming language and software environment (R Development Core Team, 2008). Critical spacing was modeled as a function of the fixed effects of the factors visual field, attention, matching, and the interaction among all three factors. Subject was defined as a random-effects factor and visual field and attention were set as random slopes. Estimates of the effect (β) and the standard error of the model coefficient (SE) are reported.

In contrast to the result from the tangential configuration, we found a main effect of attention for stimuli in a radial configuration ($\beta = .242^\circ$, $SE=.089^\circ$, $p=.009$), with critical spacing higher in the divided compared to the focused attention condition. There were no significant main effects of visual field ($\beta = -.031^\circ$, $SE=.117^\circ$, $p=.78$), or matching ($\beta = .013^\circ$, $SE=.084^\circ$, $p=.86$). There were also significant interactions between visual field and matching ($\beta = .88^\circ$, $SE=.084^\circ$, $p<.001$) and between attention and matching ($\beta = .206^\circ$, $SE=.083^\circ$, $p=.03$). There was no significant interaction between visual field and attention ($\beta = .021^\circ$, $SE=.084^\circ$, $p=.79$), nor was there a three-way interaction of attention, visual field, and matching ($\beta = .125^\circ$, $SE=.084^\circ$, $p=.14$).

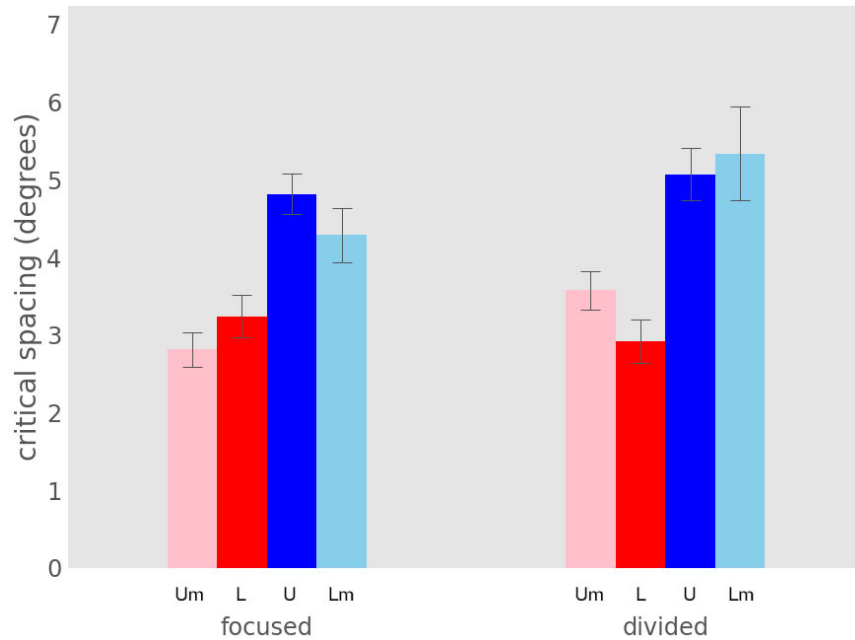


Figure 2.5 | Critical spacing for radial configuration. Upper (U), lower (L), upper matched (Um), and lower matched (Lm) critical spacing averages all plotted for both focused and divided attention conditions. Critical spacing was significantly larger in the upper compared to the lower visual field, and the lower visual field advantage is not present when matching locations based on percent of visual field extent. Error bars are between-subject standard errors of the mean.

focused attention

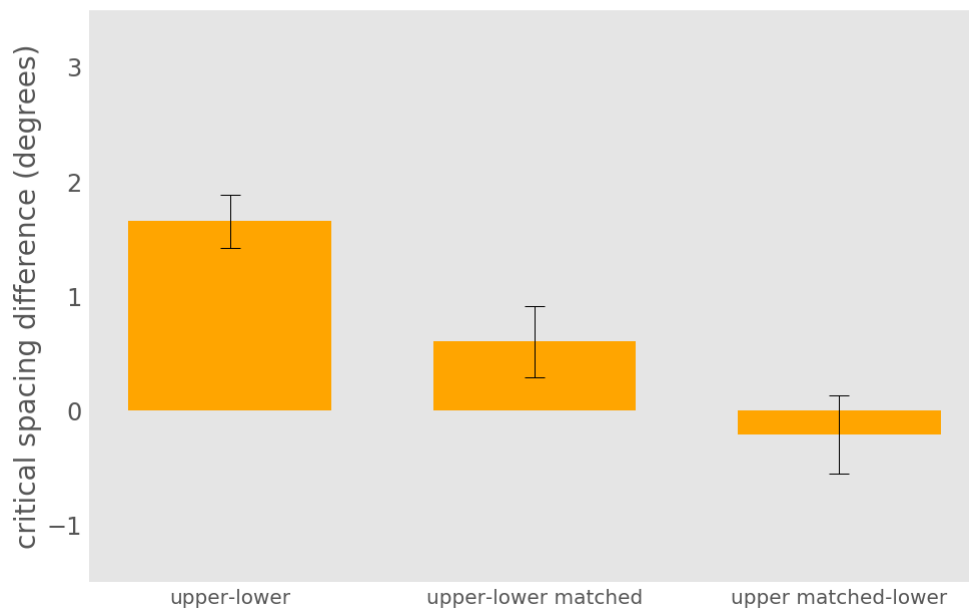


Figure 2.6 | Differences in critical spacing (focused attention condition). There was a significant difference between critical spacing in the upper and lower visual field but no difference between Upper and Lower Matched conditions or between Upper Matched and Lower conditions. Error bars are within-subject standard errors of the mean.

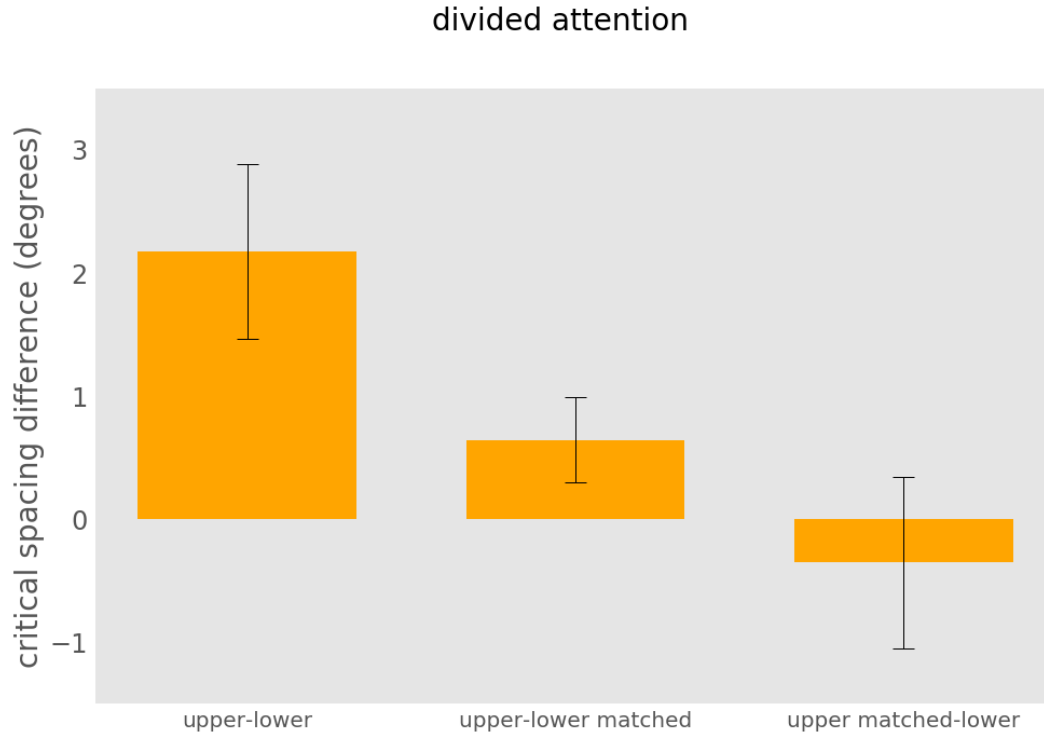


Figure 2.7 | Differences in critical spacing (divided attention condition). There was a significant difference between critical spacing in the upper and lower visual field but no difference between Upper and Lower Matched conditions or between Upper Matched and Lower conditions. Error bars are within-subject standard errors of the mean.

We assessed the relationship between visual field and matching for percentage of VFE using paired t-tests. In the focused attention condition, we observed a significantly smaller critical spacing in the lower than in the upper visual field ($t(19)=7.06$; $p<0.001$) when stimuli were presented at the same eccentricity. In contrast, critical spacing was not significantly different between the upper 8 degrees and lower matched % VFE ($t(14)=1.91$; $p=.08$) or between the lower 8 degrees and upper matched % VFE ($t(20)=-.63$; $p=.53$) (Figure 2.5, Figure 2.6). In the divided attention condition we observed a significant lower visual field advantage ($t(9)=3.05$, $p=.013$). Critical spacing was not significantly different between the upper 8 degrees and lower matched % VFE ($t(6)=.512$; $p=.62$) or between the lower 8 degrees and upper matched % VFE ($t(15)=1.85$; $p=.08$) (Figure 2.5, Figure 2.7).

We also performed paired t-tests to analyze the interaction between matching and attention. We found no significant difference between the focused and divided attention conditions in the upper visual field ($t(10)=-1.56$, $p=.15$), in the lower visual field ($t(17)=-.058$, $p=$

.954), in the upper matched % VFE ($t(15)=1.83$, $p=.08$), or in the lower matched %VFE ($t(11)=2.17$, $p=.052$).

2.4c Correlations between visual field and critical spacing asymmetries

Fortenbaugh et al. (2015) reported a correlation between the upper/lower VFE ratio and the upper/lower performance ratio in crowding across participants. We therefore tested for analogous correlations between upper/lower visual field critical spacing ratio and upper/lower visual field extent ratios. We computed these correlations on the unmatched and focused attention trials in order to make it as similar as possible to the analysis described in Fortenbaugh et al. (2015). We did not observe a correlation between asymmetry in critical spacing and asymmetry in visual field shape across participants for either tangential ($r=.034$; $p=.89$; Figure 2.8) or radial ($r=.032$; $p=.89$; Figure 2.9) configurations.

There are several potential explanations for why we did not replicate the correlation between upper/lower asymmetries in visual field extent and behavior described by Fortenbaugh et al. (2015). One explanation is that we measured critical spacing at 12 degrees in the tangential condition and 8 degrees in the radial condition in the present study, while Fortenbaugh et al. (2015) measured performance (percent correct) at 20 degrees eccentricity.

Another possibility is that critical spacing is a less consistent or reliable behavioral measure than percent correct, as calculation of critical spacing requires fitting a psychometric function to the data, while percent correct is a simple summary measure of the combined trials. To test this possibility, we conducted a split-half analysis in which we randomly divided the unmatched, focused attention trials from the tangential experiment (these are the trials most comparable to those in Fortenbaugh et al., 2015) into two equal portions for each subject and recomputed critical spacing for each of the half data sets. We repeated this process 2000 times and then correlated the critical spacing values from each half data set with the critical spacing value from the other half data set for each of the 2000 repetitions. High correlation values indicate a more reliable behavioral measure: that is, regardless of which half of the trials was selected, the computed critical spacing values were similar.

For critical spacing, the mean Pearson's r -value in the tangential condition was moderate in the upper ($r=.53$; Figure 2.10a) visual field and lower ($r=.56$; Figure 2.10b) visual fields. We conducted a similar split-half analysis of the percent correct data from the 150 ms, focused attention, unmatched, crowded trials in the Fortenbaugh et al. (2015) study. Compared to the results from the present study, the mean correlation from the Fortenbaugh et al. data was smaller in the upper visual field ($r=0.29$; Figure 2.10c) and comparable in the lower ($r=0.62$; figure 2.10d) visual field. Thus, the fact that Fortenbaugh et al. (2015) observed significant correlations between the magnitude of the lower visual field advantage in crowding and asymmetry in visual shape, but that analogous correlations for critical spacing were not observed in the present study, is not due to differences in reliability or consistency between the two behavioral measures of crowding (percent correct and critical spacing).

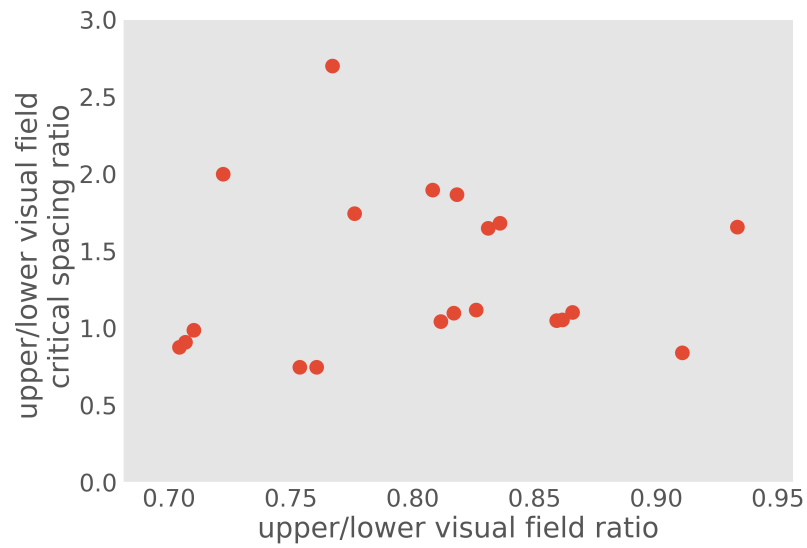


Figure 2.8 | There was no detectable correlation between visual field extent ratio and upper/lower VF critical spacing ratio for unmatched, focused attention trials in the tangential configuration.

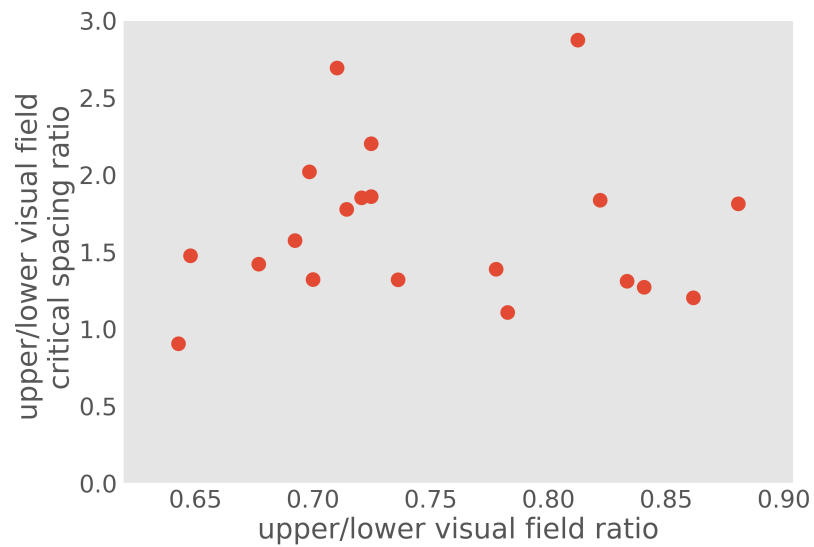


Figure 2.9 | There was no detectable correlation between visual field extent ratio and upper/lower VF critical spacing ratio for unmatched, focused attention trials in the radial configuration.

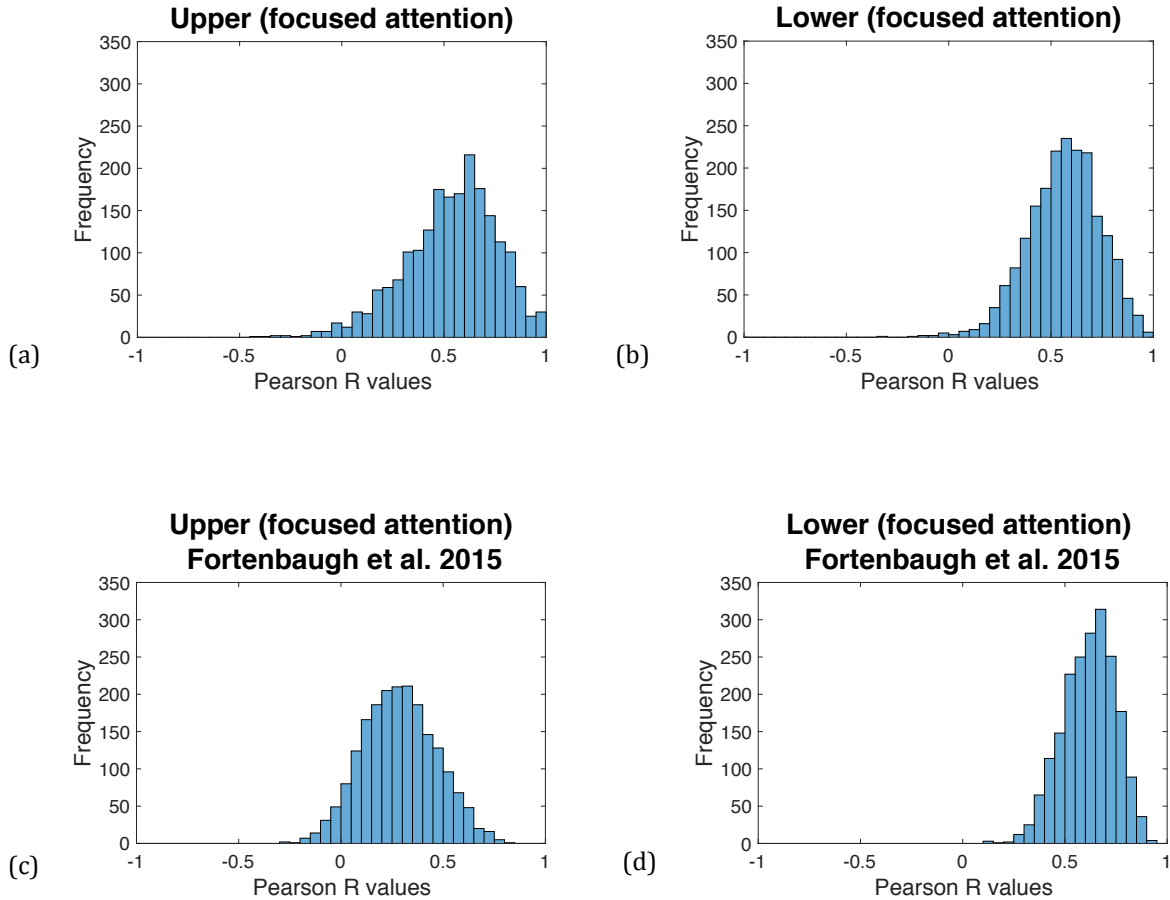


Figure 2.10 | Distributions of split-half correlation values. (a) Tangential experiment; upper visual field. (b) Tangential experiment; lower visual field. (c) Fortenbaugh et al. 2015; upper visual field. (d) Fortenbaugh et al. 2015; lower visual field.

2.5 General Discussion

The results from the first experiment show that for crowded stimuli with tangential flankers, there is no lower visual field advantage for critical spacing when stimuli are placed at the same eccentricity. This is not consistent with previous experiments showing a lower visual field advantage for overall performance (percent correct) on a crowding task (Fortenbaugh et al., 2015; He et al., 1996). One reason for this may be that we are measuring too close to fixation to observe a significant lower visual field advantage for stimuli with tangential flankers. Previous studies by Fortenbaugh et al (2015) and He et al. (1996) presented stimuli at 20 degrees in the periphery.

The second experiment shows that there is a lower visual field advantage for critical spacing when flankers were arranged in a radial configuration surrounding the target grating and placed at the same eccentricity. The second experiment was necessary because critical spacing differs depending on the configuration of the flankers. Toet and Levi (1992) found that critical spacing is smaller when flankers are configured tangentially than when they are configured

radially. According to Bouma's Law (Bouma, 1970), critical spacing scales with eccentricity and is about half the size of the distance from fixation, the stimuli Bouma used were presented in a tangential configuration. Toet and Levi (1992) found that when flankers are tangentially configured, critical spacing can be as small as 10 percent of eccentricity and when they are configured radially, critical spacing is half the size of eccentricity. Smaller critical spacing for tangential compared to radial configurations has also been observed for both letters and objects (Wallace and Tjan, 2011).

Our results demonstrate that for radially configured stimuli, critical spacing in the upper and lower visual field is dependent on differences in visual field shape and not just eccentricity as measured in degrees of visual angle. In fact, there was no measurable lower visual field advantage for critical spacing when stimulus locations were matched in units of percentage visual field extent.

We did not observe an effect of endogenous attention in the tangential experiment. However, we observed a significant main effect of attention in the radial experiment, which suggests that the effect of spatial attention may be different for radially and tangentially configured stimuli. In the tangential experiment, although subjects knew the target/flanker location on every trial in the focused condition and had to split their attention across two widely spaced locations in the divided condition, it is possible that for the tangential study, there were insufficient demands on attention in the divided attention condition. Additionally, the literature on attention and critical spacing does not lead to a clear conclusion on whether attention has an effect on critical spacing. Some studies that used pre-cuing as a means to direct attention and study the effect of attention on critical spacing found no significant effect of attention on critical spacing (Scolari et al., 2007; Nazir et al, 1992) while another study found that directing attention using a peripheral pre-cue decreases critical spacing (Yeshurun & Rashal 2010). Studies utilizing color pop-out, show a decrease in crowding and critical spacing when the target is a different color or surrounded by a different color than the distractors or flankers (Poder 2007; Scolari, Kohnen, Barton, & Awh 2007).

We were unable to replicate the finding of Fortenbaugh et al. (2015) that upper/ lower visual field ratios correlated with upper/lower visual field behavioral ratios across individuals. However, it should be noted that there were multiple differences between this study and that of Fortenbaugh et al. (2015). The most obvious difference is that we measured critical spacing while Fortenbaugh et al. (2015) used a percent correct measure. Our split-half correlations analyses indicate that there were not substantial differences in the reliability or consistence of percent correct versus critical spacing measures of crowding of gratings. Another difference is that we measured critical spacing at 12 degrees for the tangential experiment and 8 degrees for the radial experiment, whereas Fortenbaugh et al. (2015) measured crowding at 20 degrees eccentricity. It may be that the relationship between lower visual field advantage and visual field shape is more stable for crowding measurements obtained from stimuli further in the periphery.

Chapter 3:

Neither cholinergic nor dopaminergic enhancement improve spatial working memory precision in humans

3.1 Abstract

Acetylcholine and dopamine are neurotransmitters that play multiple important roles in perception and cognition. Pharmacological cholinergic enhancement reduces excitatory receptive field size of neurons in marmoset primary visual cortex and sharpens the spatial tuning of visual perception and visual cortical fMRI responses in humans. Moreover, previous studies show that manipulation of cholinergic or dopaminergic signaling alters the spatial tuning of macaque prefrontal cortical neurons during the delay period of a spatial working memory (SWM) task and can improve SWM performance in macaque monkeys and human subjects. Here, we investigated the effects of systemic cholinergic and dopaminergic enhancement on the precision of SWM, as measured behaviorally in human subjects. Cholinergic transmission was increased by oral administration of 5 mg of the cholinesterase inhibitor donepezil, and dopaminergic signaling was enhanced with 100 mg levodopa/10 mg carbidopa. Each neurotransmitter system was separately investigated in double-blind placebo-controlled studies. On each trial of the SWM task, a square was presented for 150 ms at a random location along an invisible circle with a radius of 12 degrees of visual angle, followed by a 900 ms delay period with no stimulus shown on the screen. Then, the square was presented at new location, displaced in either a clockwise or counterclockwise direction along the circle. Subjects used their memory of the location of the original square to report the direction of displacement. SWM precision was defined as the amount of displacement corresponding to 75% correct performance. We observed no significant effect on SWM precision for either donepezil or levodopa/carbidopa. There was also no significant effect on performance on the SWM task (percent correct across all trials) for either donepezil or levodopa/carbidopa. Thus, despite evidence that acetylcholine and dopamine regulate spatial tuning of individual neurons and can improve performance of SWM tasks, pharmacological enhancement of signaling of these neurotransmitters does not substantially affect a behavioral measure of the precision of SWM in humans.

3.2 Introduction

Spatial working memory (SWM) refers to the short-term storage of locations of items not currently present in the environment for immediate use. The limits on working memory can be quantified by measuring capacity (the amount of information that can be remembered) as well as precision (the fidelity with which the memorized information is recalled). In the domain of visual SWM, precision is often quantified as the average distance in the visual field between the encoded location and the location reported during retrieval.

Neural correlates of SWM precision have been described in macaque dorsolateral prefrontal cortex (dlPFC). Here, neurons exhibit sustained spiking activity during a delay period between encoding and retrieval, and the magnitude of this activity varies as a function of the remembered location (Funahashi et al., 1989). The spatial tuning of these neurons is analogous to neuronal receptive field size for visually-evoked responses, but the fact that it is associated with

a delay period with no visual stimulation distinguishes this memory-related activity from sensory responses.

We employed a pharmacological approach to explore the relationships between a behavioral measure of the precision of SWM and the spatial tuning of sensory responses and visual perception. Acetylcholine is an endogenous neurotransmitter that increases the spatial resolution of visual representations. Specifically, pharmacologically increasing cholinergic signaling reduces excitatory receptive field size in marmoset V1 neurons (Roberts et al., 2005) and decreases the spatial spread of excitatory fMRI responses to visual stimulation in human early visual cortex (Silver et al., 2008). In addition, cholinergic enhancement with the cholinesterase inhibitor donepezil causes changes in visual perception that are consistent with a reduction in excitatory receptive field size (Kosovicheva et al., 2012; Gratton et al., 2017). Moreover, administration of acetylcholine receptor agonists improves spatial tuning of delay period activity in dlPFC neurons and performance on a SWM task in macaque monkeys (Yang et al., 2013; Sun et al., 2017).

Dopamine is another neurotransmitter that has been implicated in regulation of tuning of spatial representations in the brain and SWM. In particular, local administration of drugs that act at D1 dopamine receptors can sharpen the spatial tuning of delay period activity in dlPFC neurons in macaque monkeys performing a SWM task (Williams and Goldman-Rakic, 1995; Vijayraghavan et al., 2007), and some studies have reported improved performance on SWM tasks in humans following administration of dopamine receptor agonists (Luciana et al., 1992; Luciana and Collins, 1997; Müller et al., 1998).

Given these enhancing effects of cholinergic and dopaminergic drugs on spatial representations in visual cortex, visual perception, and working memory, here we asked whether systemically increasing cholinergic transmission with donepezil and dopaminergic transmission with the dopamine metabolic precursor levodopa improves the spatial precision of working memory representations, as measured behaviorally in healthy human subjects.

3.3 Methods

3.3a Participants

The Committee for the Protection of Human Subjects at the University of California, Berkeley, approved all experimental procedures, and all participants provided written informed consent in accordance with the Declaration of Helsinki before the study began. All subjects reported normal visual acuity, either with or without optical correction. Nineteen participants (four males and fifteen females) completed the donepezil study, and twenty (six males and fourteen females) completed the levodopa/carbidopa study. One female subject from the donepezil study and two female subjects from the levodopa/carbidopa study were excluded from the analyses because their calculated SWM thresholds were greater than the maximum displacement we tested (described in Stimuli and Task section below).

Subjects were not enrolled in the study if they reported that they smoked tobacco, were taking any drugs that could affect cholinergic (for the donepezil study) or dopaminergic (for the levodopa/carbidopa study) function, or had a history of substance abuse, heart arrhythmia or heart problems, neurological or psychiatric illness, or liver disease. Because levodopa/carbidopa can reduce blood pressure, blood pressure was measured just before administration of

levodopa/carbidopa (or placebo). Participants were required to have a resting blood pressure reading between 100/60 and 140/90 mmHg and a pulse rate above 60 bpm to continue in the experiment. Participants' ages ranged from 18 to 27 (donepezil study) and from 19 to 31 (levodopa/carbidopa study).

3.3b Pharmacology

We employed a double blind within-subject experimental design in which each subject ingested either placebo or an active drug (5 mg donepezil for the acetylcholine study; 100 mg levodopa/10 mg carbidopa for the dopamine study) on different days. Carbidopa was co-administered in order to inhibit peripheral metabolism of levodopa, thereby allowing more levodopa to cross the blood-brain barrier (Olanow et al., 2000). There were three experimental sessions per subject. For the initial baseline session, subjects were acclimated to the SWM task, and no pill was administered. Data from the baseline session were used to optimize the stimuli for each subject in the subsequent pharmacological sessions.

At the beginning of the second session, subjects ingested either a drug or placebo pill, and at the beginning of the third session, subjects ingested whichever pill (drug or placebo) they did not take during the second session. Participants waited three hours after ingesting donepezil and 45 minutes after ingesting levodopa/carbidopa to begin the SWM task, intervals that correspond to the time to reach peak plasma concentration after oral ingestion for each drug (donepezil: Rogers and Friedhoff, 1998; levodopa/carbidopa: Olanow et al., 2000). The third session occurred at least two weeks after the second session to allow the drug to be completely eliminated from the body before further testing. The half-life of donepezil is 80 hours (Rogers and Friedhoff, 1998), and the half-life of levodopa/carbidopa is 1-2 hours (Olanow et al., 2000; Nyholm et al., 2012). The order of drug/placebo administration in the two sessions was counterbalanced for each of the two studies (acetylcholine and dopamine).

3.3c Stimuli and Task

Each trial began with a 1000 ms period of central fixation on a 1x1 degree white 'X' at the center of the screen, followed by 150 ms presentation of the stimulus to be encoded: a 1x1 degree red square presented 12 degrees of visual angle from fixation (Figure 3.1). Following a 900 ms delay period, the stimulus was displaced from its randomly selected original location, in either a clockwise or counterclockwise direction along the circle. This probe stimulus remained on the screen until the subject made a response. Subjects responded by pressing the "1" key on a keypad for counterclockwise and "2" for clockwise displacement, and auditory feedback was provided to indicate whether the response was correct or incorrect, followed immediately by the beginning of the 1000 ms fixation period of the next trial.

Testing was conducted in a light attenuated room. Stimuli were presented on a NEC Multisync FE992 CRT monitor with a screen resolution of 1280 by 1024 and a refresh rate of 75 Hz using Psychopy software (Peirce, 2009). Subjects viewed the monitor at a distance of 50 cm, and a chin and forehead rest kept the head position stabilized.

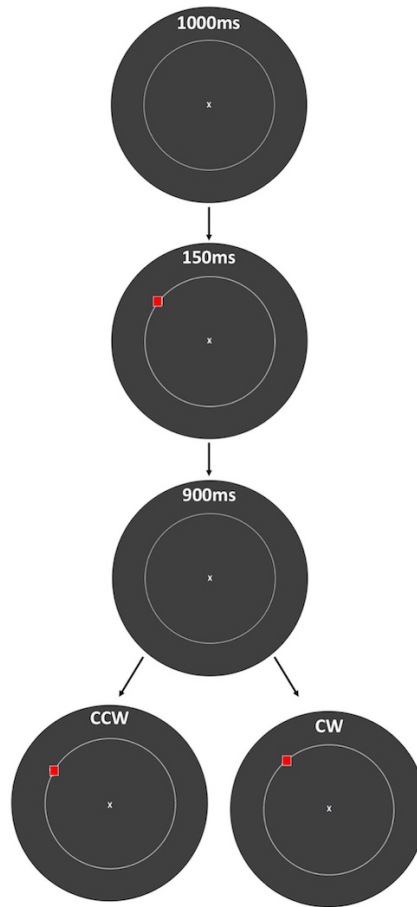


Figure 3.1 | Spatial working memory task. At the beginning of each trial, subjects viewed a fixation point for 1 second. A red square was then presented for 150 ms, followed by 900 ms of a blank screen and then presentation of the same red square, displaced either clockwise (CW) or counterclockwise (CCW) from its original location along a circle. Auditory feedback (150 ms) was given immediately after the response was made, followed by the beginning of the next trial began. The amount of displacement was defined as the polar angle between the two red squares (10 degrees in this example), and subjects indicated the direction of displacement with a button press. The circle is displayed in this figure to indicate the set of possible stimulus locations, but it was not visible to the subjects.

There were 120 possible locations for the stimulus to be remembered, all of which were on an invisible circle with a 12-degree radius. A circular aperture was attached to the front of the screen so that subjects could not use the corners or edges of the monitor frame as spatial cues during the SWM task. Subjects were instructed to maintain central fixation throughout the trial, and the experimenter monitored their eye position with an infrared camera. If fixation was not maintained during the trial, the experimenter reminded the subject to maintain fixation, and that trial was excluded from analysis and not repeated. The 1000 ms fixation period for the next trial then began. On average, 0.29% of trials were excluded due to failure to maintain fixation.

We conducted a control experiment to determine the size of the window for which the two experimenters who conducted the SWM experiments were able to reliably detect eye movements. In this control experiment, the subject fixated for 1 second, and then a 0.5 degree diameter circle was presented at 0.5, 1, 1.5, 2, or 2.5 degrees eccentricity from fixation for 500 ms. For half of the trials, the circle was red, indicating to the subject that he or she should make an eye movement to the stimulus location and then immediately back to the fixation point. For the remaining trials, the stimulus was blue, indicating that the subject should maintain central fixation. The experimenter then reported whether an eye movement had occurred or not, based on the infrared video of the subject's eye. At each eccentricity, there were 120 possible stimulus locations that comprised an invisible circle. Psychometric functions of percent correct trials versus stimulus eccentricity were computed, and Weibull functions were fit to these functions to determine the eccentricity corresponding to 75% correct performance (2.1 degrees of visual angle for experimenter 1 and 1.6 degrees for experimenter 2). Across all eccentricities, the mean hit rate was 61%, and the mean correct rejection rate was 75%. These data were not used as a part of the experiment, however they describe the accuracy of our eye-tracking procedure. It should be noted that we used a 500 ms stimulus presentation time in this control experiment instead of the 150 ms stimulus duration used in the SWM experiments, as 150 ms is not enough time for the subjects to make an eye movement to the target while it was still being displayed. This 150 ms stimulus duration was selected to discourage eye movements to the stimulus to be remembered during the SWM task.

During the SWM experiment, participants were encouraged to take breaks whenever they wanted to, and they communicated this by either withholding their response or informing the experimenter, who would then pause the experiment after the subject's response. Additionally, the experimenter explicitly asked participants if they wanted to take a break every time they had completed 20% of the trials.

For the baseline session, the set of displacements was 0.3, 1, 2, 3, 4, 6, 8, and 12 degrees (defined as the polar angle between the encoded stimulus and the probe). Performance was plotted as a function of this displacement angle (Figure 3.2), and the threshold from the resulting psychometric function was defined as the displacement corresponding to 75% correct for the fitted function. We used Palamedes Toolbox for Matlab (Prins and Kingdom, 2009) to compute values for the free parameters of alpha (threshold), beta (slope), and lambda (lapse rate, or the proportion of incorrect responses for trials with very large displacements, bounded at 0 and 1).

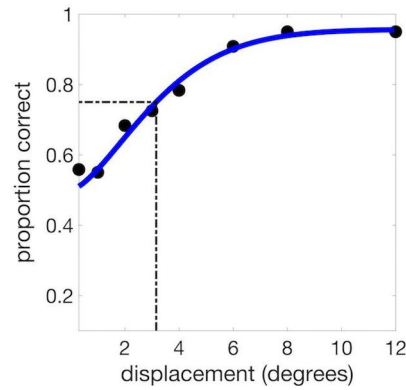


Figure 3.2 | Example psychometric curve from a single experimental session. We used the psychometric function to calculate the threshold at 75% correct (3.15 degrees in this example).

For the pharmacology sessions, displacements ranged from 0.3 to 12 degrees of polar angle, with the intervening displacements at 10%, 30%, and 60% above and below the subject's threshold (computed from the baseline session). The baseline session had 960 trials, and the pharmacology sessions had 1080 trials each. Due to experimenter error, for a subset of the participants (ten in the donepezil study and seven in the levodopa/carbidopa study), data were not collected at a displacement of 60% above threshold. In order to estimate the effect of this missing data, we removed the 60% above threshold data point from those subjects with a complete data set and then recomputed the thresholds. We found that there was no significant difference between thresholds calculated from the complete data set and those from the data that were missing the 60% above threshold value ($t(37)=-1.49$, $p=.14$). We therefore included all collected data in our analyses.

3.4 Results

To assess stability of SWM precision across multiple testing sessions, we compared threshold displacement (measured in units of degrees of polar angle) for the two pharmacology sessions in each study (acetylcholine and dopamine) using paired t-tests. Half of the subjects in each study received the drug in the first session and placebo in the second, and the other half were administered placebo in the first session and the active drug in the second. We found no significant difference in threshold between Day 1 and Day 2 for either donepezil ($t(17)=.10$, $p=.73$) or levodopa/carbidopa ($t(17)=.49$, $p=.12$) (Figure 3.3), indicating that performance was stable and that no measurable learning occurred between the first and second pharmacology sessions.

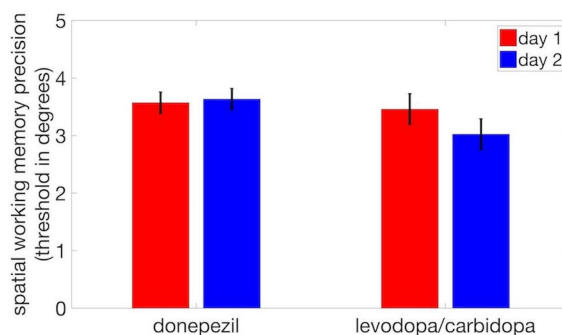


Figure 3.3 | No evidence of practice effects on spatial working memory precision. We observed no significant difference in thresholds between day 1 and day 2. Error bars are within-subject standard errors of the mean (SEM).

We observed no significant difference in SWM precision thresholds between donepezil and placebo ($t(17)=-.25$, $p=.81$) or between levodopa/carbidopa and placebo ($t(17)=.80$, $p=.44$) (Figure 3.4). Thus, even though acetylcholine regulates neuronal receptive field size, perceptual measures of spatial tuning, and the spatial tuning of mnemonic responses in dlPFC, cholinergic enhancement with donepezil had no detectable effect on the spatial precision of SWM. Similarly, although local administration of dopaminergic drugs modulates the spatial tuning of dlPFC neurons during performance of an SWM task, we found that systemic administration of levodopa/carbidopa did not significantly alter a behavioral measure of SWM precision.

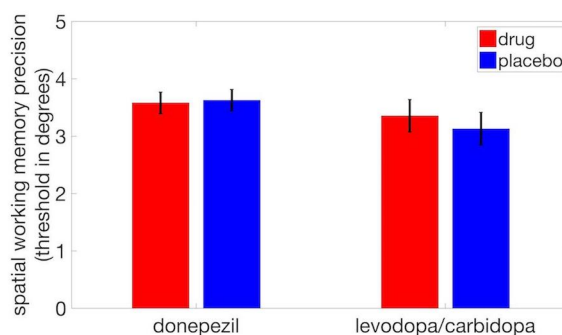


Figure 3.4 | Neither donepezil nor levodopa/carbidopa significantly affected displacement threshold on the spatial working memory task. Error bars are within-subject SEM.

We also examined the effects of cholinergic and dopaminergic enhancement on overall task performance (percent correct) and again observed no significant drug effects (donepezil: $t(17)=.46$, $p=.65$; levodopa/carbidopa: $t(17)=.50$, $p=.62$) (Figure 3.5A). The absence of drug effects was not due to ceiling effects on performance. Average percent correct values and standard deviations across all displacements in the donepezil study were 73.3 +/- 3.0% in the placebo condition and 74.0 +/- 3.0% in the donepezil condition. In the levodopa/carbidopa study, these values were 73.9 +/- 3.3% under placebo and 74.0 +/- 2.5% under levodopa/carbidopa. In addition, across both studies, mean overall performance ranged from approximately chance

levels at the smallest displacement (53% at 0.3 degrees) to nearly perfect at the largest displacement (95% at 12 degrees), indicating that the range of displacements we used was large enough to accurately measure SWM precision.

Finally, there were no detectable effects of either donepezil ($t(17)=1.21$, $p=.24$) or levodopa/carbidopa ($t(17)=0.50$, $p=.62$) on lapse rate (Figure 3.5B), a parameter of the fitted psychometric function that corresponds to the proportion of trials for which subjects responded incorrectly at the highest displacements.

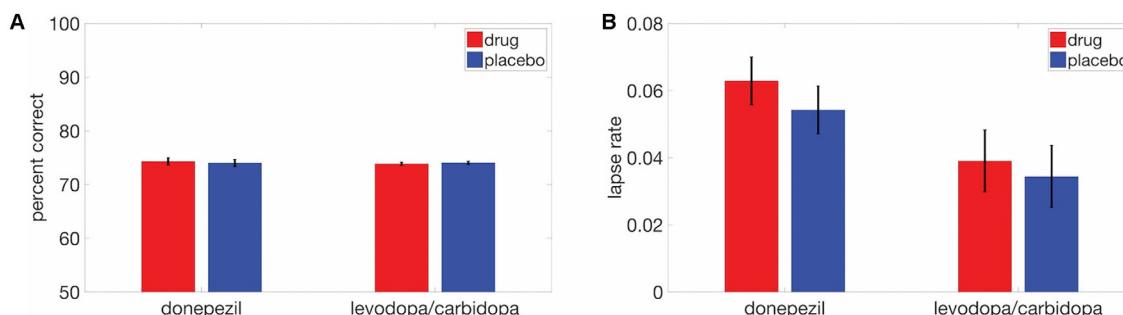


Figure 3.5 | Neither donepezil nor levodopa/carbidopa significantly affected (A) overall performance or (B) lapse rate. Error bars are within-subject SEM.

Both cholinergic and dopaminergic drugs can exhibit inverted-U-shaped dose-response functions (reviewed in Bentley et al. (2011) for acetylcholine and Cools and D'Esposito (2011) for dopamine). In addition, baseline performance on a working memory task has been shown to predict whether systemic administration of a dopaminergic drug enhances or impairs performance relative to this baseline (Kimberg et al., 1997; Kimberg and D'Esposito 2003). Moreover, individual differences in striatal dopamine synthesis capacity are correlated with working memory capacity (Cools et al., 2008), and individual differences in accuracy on a working memory task are predicted by a polymorphism in the dopamine beta-hydroxylase gene (Parasuraman et al., 2005), which codes for an enzyme that metabolizes dopamine. These findings raise the possibility that individual differences in SWM precision at baseline may reflect differences in cholinergic and/or dopaminergic tone that could influence drug effects on SWM precision.

We therefore correlated the baseline threshold for each subject with a contrast index for each study $((\text{SWM placebo threshold} - \text{SWM drug threshold}) / (\text{SWM placebo threshold} + \text{SWM drug threshold}))$. This contrast index will have a value of zero when the drug has no effect on displacement threshold, positive values when the drug enhances precision (decreases threshold), and negative values when the drug reduces precision (increases threshold). This correlation was not significant for either donepezil ($r=.19$, $p=.45$) or levodopa/carbidopa ($r=-.06$, $p=.81$) (Figure 3.6).

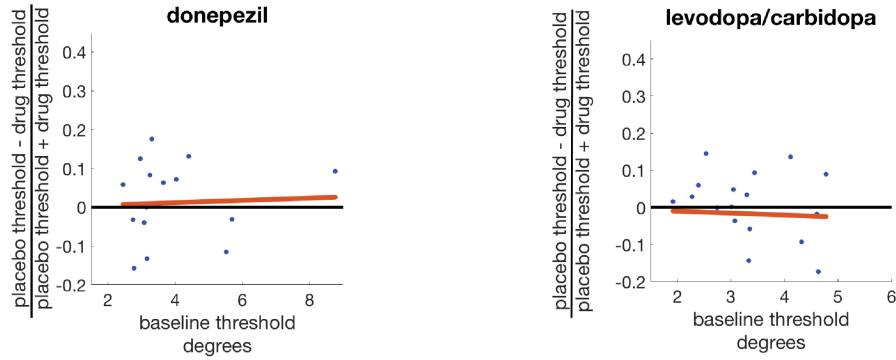


Figure 3.6 | Baseline SWM precision does not predict the effects of either donepezil or levodopa/carbidopa on SWM precision.

Finally, we explored whether SWM precision varies across different locations in the visual field. There is a well-established lower visual field advantage in performance for a variety of visual perception tasks (He et al., 1995; Rubin et al., 1996; Abrams et al., 2012; Fortenbaugh et al., 2015). We therefore plotted SWM precision as a function of visual field location (based on the stimulus to be encoded), binned into eight regions, each comprising 45 degrees of polar angle (Figure 3.7). Data from placebo and drug sessions were combined for these analyses. Overall, there were no significant differences between SWM precision in the upper and lower halves of the visual field ($t(35)=-.70$, $p=.48$) or between the left and right hemifields ($t(35)=-1.25$, $p=.21$). Lower visual field advantages in perception have often been measured for stimuli on or near the vertical meridian (He et al., 1996; Fortenbaugh et al., 2015). We therefore compared SWM precision in the upper and lower visual fields using only trials with stimulus locations within 22.5 degrees of the vertical meridian and again found no significant difference ($t(35)=.71$, $p=.47$).

The oblique effect is another well-studied anisotropy in visual perception across visual field locations (Appelle, 1972; Rokem and Silver, 2009), characterized by enhanced perception along the cardinal compared to the oblique axes of the visual field. We therefore tested for an oblique effect in SWM precision. We observed significantly greater SWM precision for locations near (within 22.5 degrees of polar angle) the cardinal compared to the oblique axes ($t(35)=2.24$, $p=.03$). However, there were no significant differences in the magnitude of the drug effect (placebo SWM threshold - drug SWM threshold) between the oblique and the cardinal axes for either donepezil ($t(17)=-1.21$, $p=.23$) or levodopa/carbidopa ($t(17)=1.52$, $p=.15$).

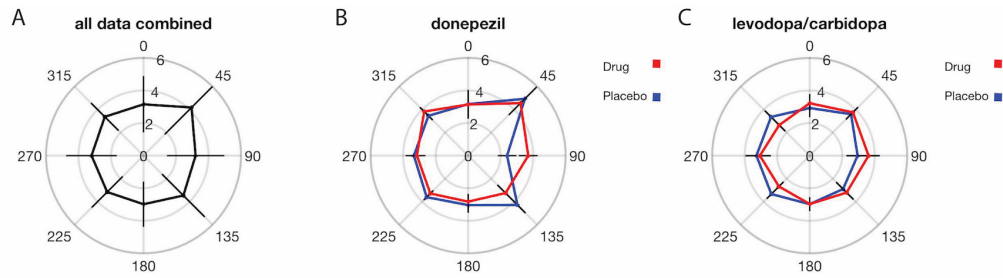


Figure 3.7 | SWM precision threshold (in degrees of displacement) does not significantly vary across the visual field, and there were no detectable effects of either donepezil or levodopa/carbidopa on SWM precision at any visual field location. Error bars are standard deviations in panel (a) and within-subject SEM in panels (b) and (c).

3.5 Discussion

The purpose of this study was to investigate the effects of cholinergic and dopaminergic enhancement on SWM precision, using the cholinesterase inhibitor donepezil and the dopamine metabolic precursor levodopa, respectively. We found no detectable effects of enhanced acetylcholine and dopamine signaling on either SWM precision or task performance.

3.5a Acetylcholine

At the single neuron level, local administration of acetylcholine reduces excitatory receptive field size in marmoset V1 (Roberts et al., 2005), thereby enhancing the spatial resolution of visually-evoked responses. At the population level, reduced receptive field size corresponds to decreased spatial extent of visual responses in retinotopic visual cortical areas, and this is what was found for fMRI responses in early visual cortex following systemic administration of donepezil to healthy human subjects (Silver et al., 2008).

At the perceptual level, systemic administration of donepezil reduces orientation-selective surround suppression (Kosovicheva et al., 2012). In surround suppression, contrast discrimination within a target grating is impaired by presentation of a high-contrast surrounding grating, and donepezil diminished this surround suppression. The cholinergic effect on surround suppression was specific to the condition in which the target grating and surround shared the same stimulus orientation, implicating early visual cortical circuits that exhibit orientation-selective surround suppression (Blakemore and Tobin, 1972; Cavanaugh et al., 2002).

Systemic administration of donepezil also has been shown to enhance contrast discrimination of a target with flankers, but only for intermediate target-flanker distances (Gratton et al., 2017). Modeling of facilitatory and suppressive effects of the flankers indicated that donepezil improved performance by reducing the spatial extent of facilitatory target/flanker interactions, consistent with reduced excitatory receptive field size. Thus, converging lines of evidence demonstrate that acetylcholine enhances spatial precision of visual cortical neuronal representations as well as visual perception.

Acetylcholine has also been examined in SWM tasks. Lesions of cholinergic inputs to macaque dlPFC selectively impaired SWM performance but did not affect performance of decision-making and episodic memory tasks (Croxson et al., 2011). Local administration of nicotinic acetylcholine receptor agonists in macaque dlPFC increased delay period activity in a SWM task for the neuron's preferred location but not the nonpreferred location, thereby improving spatial tuning of memory-related activity (Yang et al., 2013; Sun et al., 2017). Moreover, systemic administration of the $\alpha 7$ -nicotinic acetylcholine receptor agonist PHA543613 can improve SWM task performance in macaque monkeys (Yang et al., 2013), although precision of SWM was not measured in this study. However, systemic cholinergic enhancement with the cholinesterase inhibitor physostigmine improved accuracy in a spatial attention but not a SWM task in human subjects (Bentley et al., 2004).

3.5b Dopamine

Many studies have shown that pharmacological manipulation of dopaminergic signaling through iontophoresis of dopaminergic drugs in macaque dlPFC enhances spatial tuning of delay-period activity while monkeys are performing a SWM task (Williams and Goldman-Rakic, 1995; Vijayraghavan et al., 2007). There is also some evidence that systemic administration of dopaminergic receptor agonists can improve performance on a SWM task in human subjects. Systemic administration of the D2/D1 receptor agonist bromocriptine was reported to enhance SWM but not object working memory performance (Luciana et al., 1992; Luciana et al., 1997), but other studies found no effect of systemic administration of bromocriptine on behavioral measures of SWM (Kimberg et al., 1997; Müller et al., 1998) (although Müller et al. (1998) reported improved SWM performance following systemic administration of the D1/D2 receptor agonist pergolide). Our study differed from those summarized here in that these studies measured overall accuracy or performance on a SWM task. To our knowledge, our study is the first to examine the effects of dopaminergic enhancement on a behavioral measure of SWM precision.

3.5c Methodological considerations

For our study, we selected drugs that enhance cholinergic and dopaminergic function in a manner that is highly physiologically relevant to endogenous neurotransmitter signaling. Donepezil enhances cholinergic transmission by blocking the enzyme that inactivates acetylcholine after it has been released into the synaptic cleft, thereby prolonging the effective lifetime of acetylcholine in the synapse. Levodopa is metabolically converted to dopamine through the biochemical mechanisms that generate endogenous dopamine. The actions of these drugs are therefore distinct from those of receptor agonists and antagonists that bind directly to neurotransmitter receptors and alter activity in a manner that is largely independent of ongoing endogenous neurotransmitter signaling.

Although the use of drugs that modulate endogenous signaling has the benefit of physiological relevance, it is possible that more selective pharmacological manipulations that target particular receptor subtypes (like those typically used in single-unit studies of memory-related activity in macaque dlPFC neurons) could reveal cholinergic and/or dopaminergic effects on a behavioral measure of SWM precision in humans.

The acute dose of donepezil that we used was 5 mg, corresponding to the lowest dose prescribed clinically for daily administration. While it is possible that cholinergic effects on SWM precision would be observed at higher doses of donepezil, previous studies in our lab have documented statistically significant effects of a single dose of 5 mg donepezil on spatial extent of fMRI responses in visual cortex (Silver et al., 2008), the effects of endogenous spatial attention on visual perception (Rokem et al., 2010), a behavioral measure of surround suppression (Kosovicheva et al., 2012), and the spatial extent of facilitatory target/flanker interactions in visual perception (Gratton et al., 2017). Similarly, the dose of levodopa/carbidopa that we employed was 100 mg /10 mg, and 100 mg levodopa has been shown to have significant effects on fMRI responses in the striatum to stimuli associated with punishment (Wittmann and D'Esposito, 2015), functional connectivity of fMRI signals (Kelly et al., 2009), and the magnitude of striatal reward prediction errors (Pessiglione et al., 2006).

Many cholinergic and dopaminergic drugs can produce an inverted-U-shaped dose-response function, in which a small increase in signaling can benefit task performance and increase regional brain activity, but a larger increase can cause effects in the opposite direction (reviewed in Bentley et al., 2011; Cools and D'Esposito, 2011). An inverted-U-shaped profile has also been reported for cholinergic (Yang et al., 2013) and dopaminergic (Vijayraghavan et al., 2007) effects on spatial tuning of dlPFC neuronal delay period responses. While it is possible that a different dose of donepezil or levodopa/carbidopa in our study could have produced different results, we found no significant correlation between a subject's baseline SWM precision and effects of donepezil or levodopa/carbidopa on SWM precision for that subject. This lack of correlation could indicate that individual differences in baseline cholinergic or dopaminergic tone do not predict drug effects on SWM precision. However, it is also possible that SWM precision may not be an accurate proxy for baseline cholinergic or dopaminergic tone.

It is also possible that larger sample sizes would have revealed effects of dopaminergic and/or cholinergic enhancement on SWM precision. Our analysis included complete data sets from 18 participants in each study, a sample size that is comparable to previous studies that have documented significant effects of cholinergic enhancement on perception and dopaminergic enhancement on working memory (cholinergic studies: Kosovicheva et al., (2012), 19 subjects; Gratton et al. (2017), 28 subjects; Rokem et al. (2010), 20 subjects; Bentley et al. (2004), 18 subjects; dopaminergic studies: Kimberg et al. (1997), 31 subjects; Luciana et al. (1992), 8 subjects; Müller et al. (1998), 32 subjects). We also note that our subject pool differed from that of most other studies in gender balance, as 14/18 of our subjects in the donepezil study and 12/18 in the levodopa/carbidopa study were female.

Given the observed variance in our measurements and our sample sizes, the within-subject SWM threshold difference between the placebo and drug conditions would have needed to be 0.39 degrees (10.8% change from placebo) in the donepezil study and 0.60 degrees (19.1% change from placebo) in the levodopa/carbidopa study in order to produce a significant drug effect at $p=0.05$. By comparison, the spatial spread of the excitatory fMRI response to visual stimulation was reduced by 8.5% in area V1 when subjects received donepezil compared to placebo (Silver et al., 2008). Moreover, local administration of acetylcholine reduced receptive field length of V1 neurons by 15.3% (Roberts et al., 2005). In our study, percentage change in SWM threshold was 1.3% (donepezil threshold numerically less than placebo) and 7.2% (levodopa/carbidopa threshold numerically greater than placebo).

Another consideration is that we used a delay period of 900 ms without a visual mask. In principle, persistence of the sensory response to the stimulus to be remembered could have aided subjects' performance on the SWM task. However, this type of retinal persistence, often studied in the psychological literature as iconic memory, fades after 300 ms (Sperling, 1960), an interval much shorter than our 900 ms delay period. In addition, our use of a delay period of 900 ms with no mask is consistent with several previous studies of visual and visuospatial working memory (Alvarez and Cavanagh, 2004; Vogel and Machizawa, 2004; Bo and Seidler, 2009).

Much of the evidence for cholinergic and dopaminergic effects on spatial tuning of working memory representations comes from studies of macaque dlPFC neurons. Although the SWM task we employed is very similar to that used in the macaque studies, recent evidence from human patients with lesions to dlPFC has raised questions about the homologies between humans and macaques in this region (Mackey et al., 2016). Specifically, patients with dlPFC lesions had normal accuracy on a SWM task, while patients with precentral sulcus lesions had lower accuracy when making saccades to a remembered location. However, these inaccurate saccades were typically followed by corrective saccades, indicating that the deficit in patients with precentral sulcus lesions may be in the domain of executive function rather than reduced precision of SWM representations.

These lesion results are supported by a recent transcranial magnetic stimulation study in which disruption of human dlPFC did not affect accuracy of memory-guided saccades (Mackey and Curtis, 2017). However, disruption of topographically-organized precentral sulcus and intraparietal sulcus regions impaired SWM accuracy (Mackey and Curtis, 2017) in a way that is consistent with analogous studies in macaque frontal eye fields (FEF) and lateral intraparietal area (LIP). Taken together, the data suggest that the dlPFC circuits that subserve SWM in macaque monkeys may not have a direct homolog in human dlPFC but that other frontal and parietal regions that support SWM may be more homologous in the two species. These species differences in the functional networks underlying SWM may be accompanied by neurochemical differences as well. This may account for the fact that both acetylcholine and dopamine have well documented effects on neural correlates of SWM in the macaque dlPFC but no observable effect on behavioral SWM precision in humans. An important direction for future research is to characterize cholinergic and dopaminergic effects on neural correlates of SWM in those frontal and parietal regions that appear to have functional homologies in humans and macaques.

3.5d Differences between spatial precision of perception and working memory representations

Our results support a distinction between the limits of spatial resolution in visual cortical neurons and visual perception and the corresponding limits in SWM representations. Although there are clear cholinergic effects on spatial resolution at the level of single neurons (Roberts et al., 2005), fMRI responses (Silver et al., 2008), and visual perception (Gratton et al., 2017), we found no evidence for cholinergic effects on the precision of SWM, as measured behaviorally in human subjects.

We also found no evidence for visual field asymmetries in the precision of SWM, a result that also indicates fundamental differences between the spatial resolution of perception and memory. Previous studies have documented a clear lower visual field advantage in visual crowding tasks (He et al., 1996; Fortenbaugh et al., 2015). Visual crowding refers to the reduction in discriminability of a stimulus in the peripheral visual field when it is flanked by

other stimuli. The strength of crowding depends strongly on the distance between the target and flankers, and the minimal target/flanker distance that enables a certain level of performance is known as the critical spacing, which is a measure of spatial resolution of visual perception. We have recently shown that critical spacing is smaller in the lower compared to the upper visual field (Harewood et al., 2016). In the present study, this upper/lower visual field difference was not observed for SWM precision, a measure of the spatial resolution of working memory representations.

3.6 Acknowledgments

The work presented in this chapter was published in *Frontiers in Neural Circuits* in December of 2018, Adeola Harewood Smith (the author of this dissertation) was the first author and Jnana Aditya Challa and Michael Silver were both co-authors on that manuscript. Both co-authors contributed significantly to the work in this chapter and to the original manuscript.

Chapter 4

4 Conclusion

In this dissertation we have demonstrated that visual field shape plays a role in critical spacing of crowding. The lower visual field advantage exists for critical spacing when the stimuli are placed at the same eccentricity in the radial condition, but matching stimulus locations for the same percentage of visual field extent eliminates the lower visual field advantage. These results are consistent with those previously found in crowding (He et al., 1996; Fortenbaugh et al., 2015). There was not a significant effect of attention on critical spacing for the tangential conditions but there was a significant main effect of attention in the radial condition. We did not observe a correlation between the upper/lower visual field critical spacing ratios and the upper/lower visual field extent ratios for the unmatched, focused attention condition.

We have also shown that cholinergic and dopaminergic enhancement did not improve a behavioral measure of spatial working memory precision. Moreover, we did not observe a lower visual field advantage in spatial working memory, which in combination with our findings that spatial working memory is not affected by cholinergic and dopaminergic enhancement, suggests that for spatial resolution, there may be dissociation between perception and working memory.

One reason we may not have observed a lower visual field advantage for spatial working memory is due to the absence of flankers or surrounding objects present in the spatial working memory task. In the critical spacing task, the target was flanked on either side by gratings, this required subjects to suppress the surrounding flankers in order to correctly perform the task. Future studies should directly explore the differences or similarities between spatial interactions in spatial working memory and perception.

Perception and memory are influenced by a variety of factors. In this dissertation, we have shown that at the same eccentricity, spatial resolution is different in the upper and the lower visual field for crowded stimuli with radial flankers. We have also shown that dopaminergic and cholinergic enhancement do not improve spatial working memory precision and that spatial representations in working memory are not significantly different in the upper and lower visual fields.

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