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Correlation of Central Versus Peripheral Macular Structure-Function With Acuity in Age-Related Macular Degeneration

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Purpose: Patients with advanced age-related macular degeneration (AMD) may have preserved visual function despite significant retinal structural changes. We aimed to evaluate the relationships among retinal thickness, macular sensitivity, and visual acuity (VA) in advanced AMD.

Methods: We examined 43 eyes of 22 patients with advanced AMD (ages 66–93 years), prospectively recruited from the Canberra Hospital Ophthalmology Department. Visual function was measured on participants with low and high contrast visual acuity (LCVA and HCVA) and 10-2 Matrix visual fields. Retinal structure was determined with spectral domain optical coherence tomography (OCT), and customized software mapped the 64 OCT macular thickness regions onto the 44 regions of the 10-2 test.

Results: Median retinal thickness at each 10-2 region was near normal. Just 7 of 88 regions from the OCT analysis that were thicker than the median had sensitivity that declined significantly with increasing thickness ($r = -0.698 \pm 0.082$, mean $\pm$ SD), whereas 17 of 88 thinner regions showed significantly decreasing sensitivity with decreasing thickness ($r = 0.723 \pm 0.078$). The absolute value of deviations from median optical coherence tomography thickness (aOCT) outside the central eight degrees was significantly correlated with HCVA ($r = -0.34$, $P = 0.047$). Thickness in the central eight degrees was not. Similarly, matrix sensitivities inside the central eight degrees were significantly correlated with outer aOCT ($r = -0.49$, $P = 0.002$).

Conclusions: Retinal thickness outside eight degrees were significantly associated with HCVA and macular sensitivity. These results suggest that outer macular thickness may be a useful prognostic indicator in AMD.

Translational Relevance: Retinal structure at the borders of the macula may be a surrogate marker of vision and retinal thickness near fixation.

Introduction

Age-related macular degeneration (AMD) is the leading cause of vision loss in the Western world,[1] leading to poor quality of life outcomes especially for reading, driving, and looking after oneself.[2–4] Recent advances in managing early stages of AMD[5] and treatments for end stage geographic atrophy are currently being explored (ARVO abstract: 2019, 4983). Previous studies have investigated impaired visual acuity (VA),[6] dark adaptation,[7] flicker thresholds,[8] photostress recovery time,[9] and microperimetry in AMD.[10] Traditionally, high-contrast visual acuity (HCVA) has

been used as a functional end point for clinical studies and for monitoring changes in function but is considered a poor measure of early stages of functional impairment due to the limited area of retinal function assessed, and reductions in other forms of macular function preceding changes in HCVA.[11,12] That being said, photopic vanishing optotypes may be more effective in AMD.[13] Visual acuity has also been shown to be poor in identifying ocular pathologies, such as glaucoma[14] and diabetic retinopathy.[15] Disagreement also exists in the spatial correlation between sensitivity loss, as measured by microperimetry, and morphological changes in the retina.[16,17] For instance, retinal sensitivity loss in eyes with good VA, has been demonstrated in regions with soft drusen and retinal pigmented epithelial change.[18] Regulatory agencies are recognizing the need for a more robust measure of functional change than best corrected visual acuity (BCVA) as a functional end point for retinal disease and the need for novel functional end points to be developed.[19]

In principle, combined structure/function measures might be useful. We recently published a paper on a new form of objective perimeter. That indicated that a functional marker in the peripheral macular retina might be able to predict which neovascular AMD (nAMD) eyes will respond to anti-vascular endothelial growth factor (VEGF) treatment.[20] We therefore hypothesized that a comparison of central versus peripheral retinal thickness and sensitivity might yield new and prognostically valuable information about AMD.

In patients with AMD, there are no studies investigating sectoral differences in the structure-function relationship, particularly between the center and peripheral visual field and inner/outer macular regions. As a starting point, we used the Matrix 10-2 perimeter, with its large 2 degrees square stimuli, to assess 44 regions of the central 20 degrees of the field. We used optical coherence tomography (OCT) to measure macular thickness across an 8×8 grid of locations that were 3 degrees square. We then mapped the thickness data onto the 10-2 regions allowing detailed region-by-region comparisons between structure and function. Overall, the aim of this study was to investigate the relationship between structural changes and functional loss in patients with advanced AMD presenting with a range of acuities.

Methods

This was a prospectively designed cohort study. Adult participants from the retinal clinic at the ophthalmology department at the Canberra Hospital were recruited. In addition, participants were recruited from private ophthalmology clinics and recruitment invitation to members of the Macular Disease Foundation Australia living with AMD in the Canberra region. All participants recruited completed the study. The study was approved by the Human Research Ethics Committees of the Australian Capital Territory (ACT) Health (Protocol ETH.10.13.291), and the Australian National University (protocol 2013/286), and was conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Study Participants

Twenty-two Caucasian participants with advanced AMD were included at baseline (82.3 ± 7.8 years, mean age $\pm$ SD). Sixteen were women and the participants ranged in age from 66 to 92 years. Participants were selected if they met eligibility criteria that included: (1) reported experiencing difficulties with face perception and social interactions; and (2) diagnosed by a retinal ophthalmologist (R.W.E.) as having advanced AMD, defined as nAMD or geographic atrophy in at least one eye. For grading AMD severity, we used the grading scheme adopted by Barbazetto[21] and the Age-Related Eye Disease Study Research Group.[22] Participants were recruited to achieve a wide range of VA losses (Table 1). Exclusion criteria included the history of ocular trauma or surgery, and the presence of other ocular pathologies, except for clinically nonsignificant lens opacities. In addition, cognitive dysfunction, including dementia and morbidities affecting retinal structure, were excluded. Cognitive dysfunction was identified during the initial interview with a clinical psychologist (J.L.). No participants were found to suffer from mental health impairment. Details of these participants face recognition performance and quality of life issues have been published elsewhere.[23,24]

Ophthalmic Examinations

All eligible participants underwent a comprehensive ophthalmic examination by a qualified orthoptist measuring visual function, including both high- and low-contrast BCVA (HCVA and LCVA, respectively) measured unilaterally using retro-illuminated logMAR charts conforming to the Early Treatment Diabetic Retinopathy Study (ETDRS) letter standard.[25] Room lights were turned off and letter contrasts were presented with 96% and 10% for HCVA and LCVA charts, respectively. Termination rules for acuity measurements included four or more errors

Table 1. HCVA and LCVA Indicate Best Correct High and Low Contrast Visual Acuity in ETDRS Visual Acuity Score Letters (VAS)

			Right eye							Left eye						
Patient	Sex	Age	Diagnosis	HCVA	LCVA	CRT (μm)	CRT Range (μm)	MD (dB)	PSD (dB)	Diagnosis	HCVA	LCVA	CRTs (μm)	CRT Range (μm)	MDs (dB)	PSD (dB)
mf86011	F	94	SRF	12.5*	3.5*	215	130: 315	−24.88	3.25	Classic	45*	29*	185	124: 306	−24.39	4.51
mf86012	F	93	GA	22*	13.5*	247	209: 292	−23.39	6.08	Occult	74.5*	58*	269	237: 312	−3.14	2.29
mf86013	M	87	LD	81.5*	75.5*	297	261: 342	−7.33	5.18	Classic	76.5*	51.5*	451	337: 590	−10.26	5.63
mf86014	M	71	LD	13	0	276	249: 309	−23.01	3.86	Occult	88	72	279	221: 338	−1.17	2.34
mf86015	F	74	Occult	59	49	332	253: 416	−6.19	7.35	GA	54	43	181	109: 238	−6.88	9.23
mf86016	M	89	Occult	77	54	385	307: 513	−3.97	3.1	Classic	56	29	470	355: 548	−10.83	5.62
mf86017	F	79	Classic	9.5*	2*	177	84: 241	−18.93	5.87	Occult	69*	50.5*	299	254: 370	−16.04	5.92
mf86018	M	89	Classic	72	51	262	222: 296	−2.22	4.04	Classic	34*	19*	259	219: 287	−5.96	6.81
mf86019	F	68	SRF	2.5*	0*	241	187: 303	−20.31	7.56	Classic	56	37	500	460: 525	−21.23	3.8
mf86020	F	79	Classic	81	77	221	179: 283	−4.32	2.73	LD	89	78	268	224: 317	−0.39	2.82
mf86021	F	70	Classic	70	59	213	151: 272	−11.71	11.01	Classic	1	0	466	372: 522	−20.84	7.33
mf86022	F	92	GA	26	19	246	169: 298	−13.73	8.57	Occult	56	43	279	171: 323	−8.32	5.78
mf86023	M	79	GA	58	46	109	63: 167	−9.67	6.4	GA	52	35	143	104: 207	−7.13	8.14
mf86024	F	86	GA	72	48	187	145: 238	−23	5.48	GA	65	35	131	91: 183	−21.67	8.92
mf86025	F	65	Classic	45	39	207	162: 272	−10.96	9.18	Classic	48	44	206	141: 270	−7.19	8.73
mf86026	M	81	Occult	50	45	337	241: 424	−6.33	5.47	Occult	82	60	322	283: 337	−12.76	5.2
mf86029	M	79	GA	25	19	122	97: 172	−18.36	9.05	GA	35	23	122	102: 151	−21.71	7.48
mf86033	M	89	Classic	11	1	993	808: 1184	−26.51	2.04	Classic	60	43	172	118: 239	−15.91	6.33
mf86034	M	82	Occult	44	39	175	110: 247	−15.67	11.78	GA	13	2	118	38: 188	−23.46	8.26
mf86036	F	74	Occult	85	74	393	331: 446	0.94	1.91	Occult	80	59	538	503: 602	−1.44	2.46
mf86037	F	85	GA	79	64	249	209: 282	−12.86	10.12	Classic	10	10	198	137: 257	−18.47	9.1
mf86039	F	88	GA	71	49	213	177: 261	−11.5	6.39	GA	29	16	325	158: 403	−15.76	6.54

Matrix MD and PSD are the Mean Defect of that perimeter. SD values. Mean CRT is the central retinal thickness from the Spectralis OCT, and the Range are the minimum and maximum values with that central 1 mm. The columns labeled Diagnosis indicate the predominant eye-wise diagnoses: Classic is classic CNV; GA is geographic atrophy; LD large drusen as per AREDS-3; Occult is Occult CNV; SRF is sub-retinal fibrosis secondary to pigment epithelial detachment.

*Indicates an acuity was the mean of two repeats.

on a single line.[26] Slit lamp biomicroscopy, intraocular pressure, and pachymetry were measured prior to automated perimetry with 10-2 frequency doubling technology (MATRIX) perimetry (Carl Zeiss Meditec, Dublin, CA). Its use in AMD and its threshold methods are discussed in detail elsewhere.[27] We used the auxiliary fixation targets option of the 10-2 test to aid fixation. This presents four 2-degree diameter targets at 10 degrees eccentricity from the central target. These have been shown to improve fixation significantly in similar patients with AMD to those used here.[27] Participants were subsequently dilated with 1.0% tropicamide and 2.5% phenylephrine and spectral domain OCT scans were obtained from each eye (Spectralis, HRA + OCT; Heidelberg Engineering, Heidelberg, Germany, software version 6.9.5.0). Two scan patterns were obtained. The first was a dense central volume scan (27 degrees × 27 degrees), 61 B-scans each spaced 120 µm apart, based upon an automatic real-time (ART) mean of 25 repeats of the 768 A-scans. The second was a circular 12 degrees diameter scan centered on the optic disc composed of 768 A-scans and ART mean of 100. Automated retinal segmentation was performed by Heidelberg Heyex software. The 8 × 8 grid of full retinal thickness measurements was extracted from the "Thickness-Grid" fields of the xml files recorded for the central volume scans, measured and recorded with the 7-degree fovea-disc tilt. The thickness spanned the retinal pigment epithelial to the retinal surface. All scans including segmentation were reviewed on the day (by E.M.F.R.) to confirm scan quality. The Spectralis locks all scans to the retinal vessel pattern and are rescanned in the event of fixational errors. When patients had difficulty seeing the fixation target an auxiliary target was used and was moved to align the fovea to the center of the scan. The scanned area is larger than the 8 × 8 grid so there was an opportunity for a final alignment of the grid and the fovea post hoc, after which the Heyex software calculated the mean thickness within each 8 × 8 grid region. Single-field fundus photography was taken on all participants centered on the fovea (Canon CR-2, Tokyo, Japan).

Analysis

All statistical analysis and manipulation of OCT and Matrix data was completed with custom made MATLAB code (MathWorks, Inc., Natick, MA). As is the default for Heidelberg central scans, the posterior pole scans were imaged with a 7-degree tilt. These scans produced an 8 × 8 grid of thickness values. Each grid consisted of 3 degree squares that overlapped well with 10-2 grid of 2 degree squares representing the large Matrix grating stimuli (Fig. 1A). A matrix of weights was generated to map the OCT data onto the 10-2 grid, taking into account the exact overlap of the areas of the two types of regions and the effects of the tilt. We have published the method in detail.[28] The thickness data was first flipped to be the projection into the visual field. The result was 44 retinal thickness measures that matched the 44 10-2 perimetry regions. It was useful that the Matrix stimuli were similar in size to the OCT regions so that they gave an indication of mean sensitivity over areas comparable to the regions. Spearman correlation coefficients were used to examine correlations between the OCT parameters and visual sensitivity at each region.

As might be expected, we found that reduced sensitivity was often correlated with regions of thicker or thinner than normal retina, so we took steps to accommodate this. The median thickness computed at each region (Fig. 1B) was very close to the standard for the Heidelberg OCT for normal persons at just over 300 μm peri-centrally and somewhat less in the central and peripheral regions.[29] We therefore used median results of our patients as a normative template, and calculated differences from the median thickness. For all analyses, right-eye data was flipped right-to-left for all calculations, in particular when calculating differences from the normative template (see Fig. 1B). Results for right eyes were then flipped back for presentation in all subsequent figures. To examine if functional data were correlated with overly thick or thin retinal regions, we examined the absolute value of the deviations from median OCT thickness (aOCT).

When examining correlations with HCVA and LCVA we separately analyzed the mean across the central and peripheral regional data, separating the data into: (1) the central 8 degrees field to align with the inner 16 regions (4 × 4) of the 10-2 stimulus layout and (2) the outer 2 rings of the 10-2 maps (28 regions). Before comparison with the VA data the means of these inner and outer regions was computed. This also reduced the effects of multiple comparisons given that these averages meant the 146 correlations were computed across 2 numbers per eye rather than 44.

Results

Table 1 shows the baseline clinical data for the patients included in the study. Patients with exudative AMD presented with classic (15/44 eyes) or occult lesions (11/44), with the remainder presenting with large drusen (3/44), geographic atrophy (13/44), and

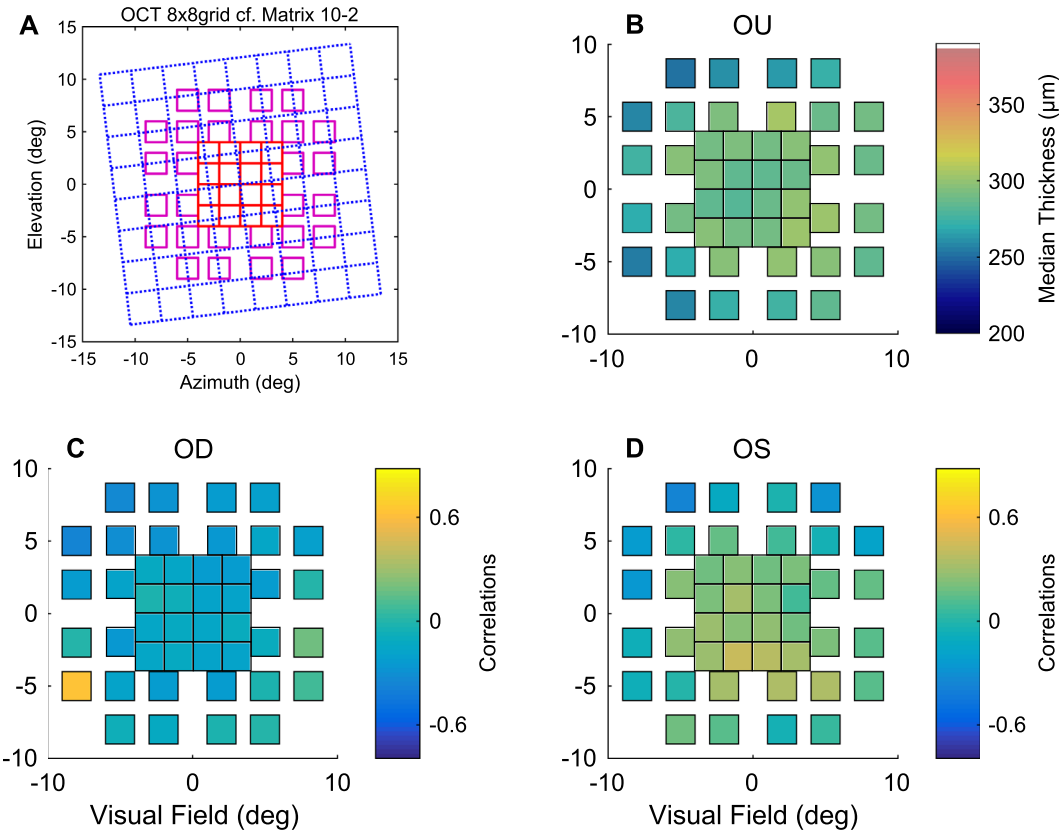

Figure 1. (**A**) Overlap of the OCT 8 × 8 thickness grid data (blue) onto the 10-2 grid: red = inner regions, magenta = outer regions. The thickness data was flipped to be the projection into the visual field. (**B**) To compute the overall median thicknesses for both eyes together (OU) the thickness data from the right eye were flipped so that anatomically equivalent regions were considered between eyes. The plotted median regional thicknesses thus represent the combined measures from both eyes of all AMD eyes, mapped onto the Matrix 10-2 test grid. (**C, D**) Correlations between the thickness data and decibel sensitivity at each 10-2 location for right and left eyes, respectively. Positive correlation indicates increasing thickness correlated with greater sensitivity. Negative correlations indicate decreasing sensitivity for increasing thickness. The correlations are modest with only one peripheral location showing significant correlation OD (**C**, *yellow check bottom left*).

subretinal fibrosis (2/44). This was reflected with mean HCVA loss of 36.5 ± 28.4 (letters) in the right eye compared to 31.7 ± 25.0 in the left eye, and greater Matrix mean deviation loss of -13.4 ± 8.06 dB in right eyes compared to -12.5 ± 7.83 dB for left eyes. The use of the auxiliary fixation aids (Methods) appeared to be validated because in the 44 measured fields the median number of fixation losses was 0 out of 10 (mean ± SD, 1.14 ± 2.12; interquartile range: 0 to 2) in agreement with the literature.[27] Not reported there was the percentage of valid pixels for the OCT thickness grid data per eye. The median ± mean absolute deviation (MAD) per eye was 99.85 ± 0.149%, and of the 2816 grid thickness values only the fifth percentile was less than 100% at 96.47%.

Figure 1A shows the overlap between the red and magenta squares representing the large Matrix grating stimuli, and the OCT 8 × 8 thickness grid (blue squares). The figure takes into account the effects of the 7-degree tilt of the OCT grid. The inner 16 regions of the Matrix grid (red) will be referred to later as the inner regions, whereas the outer 32 regions (magenta) will be referred to as the outer regions. The abundant overlap of the Matrix stimuli and OCT thickness-grid regions means mapping from one to the other is well principled. By contrast all other perimeters that provide 10-2 like test patterns use tiny 0.43 degrees diameter Goldmann Size 3 stimuli. These stimulate only 3.65% of each 2 × 2 degrees cell of the 10-2 pattern, and thus one cannot with any confidence compare the resulting sensitivity data to the 3 × 3 degrees OCT thickness grid measures. This was our main reason for selecting the Matrix with its 2 × 2 degrees stimuli. Figure 1B shows the median retinal thickness at each 10-2 location. Recall that thickness data has been flipped to the projection into the visual field.

To produce the median across eyes at each location, the right eye data was reversed to produce the left eye equivalent so that anatomically equivalent regions are considered. Figures 1C 1D show the mean correlations

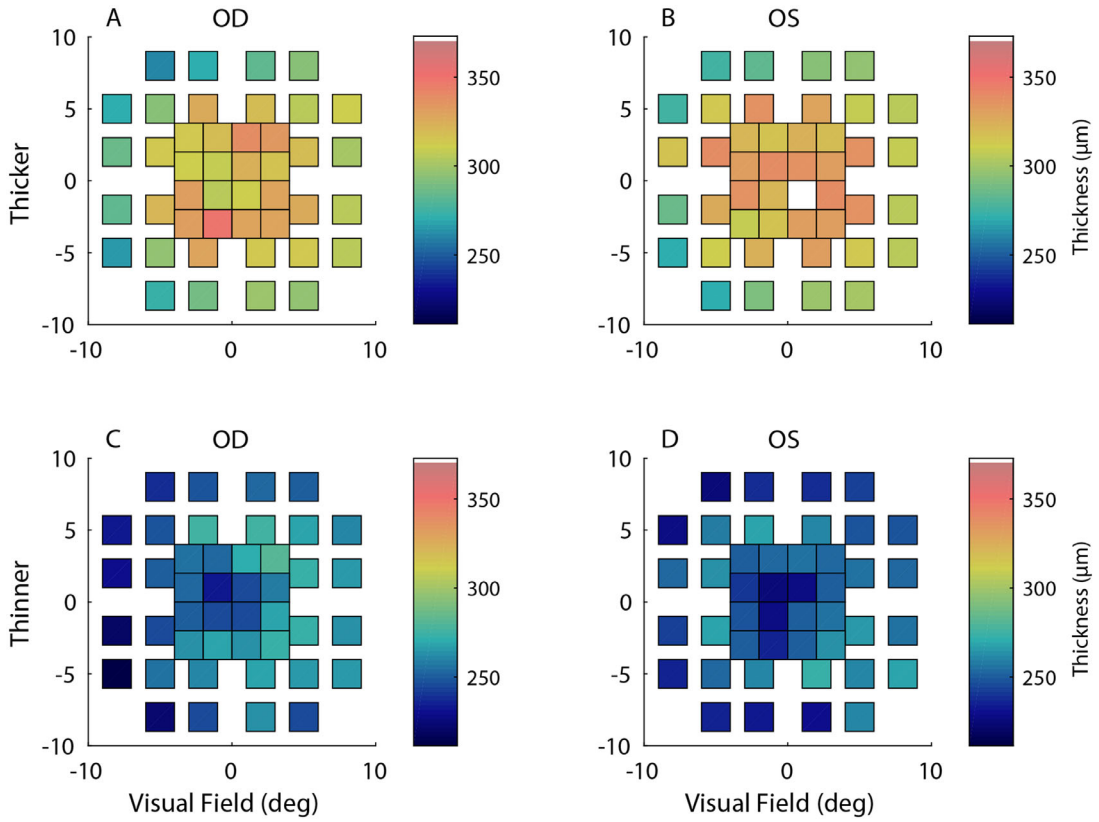

Figure 2. Median thicknesses by eye for the locations that were (**A, B**) thicker or (**C, D**) thinner than the median thickness at each region (see Fig. 1B).

between the thickness data and decibel sensitivity at each 10-2 location for the right and left eyes. Positive correlations indicate regions of increased thickness and higher sensitivity. The correlations were modest with only one peripheral location (see Fig. 1C) showing significant correlations in the right eye ($r = 0.42$, $P = 0.002$). Further examination indicated that the low correlation was in part due to interference from averaging eyes with active pathophysiological processes of retinal atrophy (thinning) and thickening, when we isolated eyes based on retinal thickness, sensitivity loss emerged as being correlated with both thicker and thinner than median macular regions.

Subsequent analysis utilized the median retinal thickness values (see Fig. 1B) subtracting that value for each region to derive deviation from the median template, which was a good proxy for normative data (Methods). For each eye, we then separately examined median regional thickness data for the locations that were thicker (Figs. 2A, 2B) or thinner (Figs. 2C, 2D) than the template.

Figure 3 shows the Matrix sensitivity profile for the same selection of regions with thicker or thinner retinal structure relative to the median. As might be expected in AMD, regions of greatest sensitivity loss were often isolated to locations near fixation (Fig. 3D). The 10-2 tests took 4.40 ± 0.15 and 4.43 ± 0.26 minutes (mean ± SD) for the left and right eyes, respectively. Figure 3 shows that the damage to the two eyes can be quite asymmetric, but this seems to affect test-duration very little.

Figure 4 shows regional correlations between the Matrix sensitivities and retinal thickness for each region. For the thicker retinal regions, there were 7 of 88 with significant negative correlations ($r = -0.698 \pm 0.082$, mean ± SD). For thinner retinal locations, 15 of 88 significant positive correlations were found ($r = 0.723 \pm 0.078$). The cutoff for significant correlation was very close to ±0.6 in all regions. The presentation within the central 8 degrees (the central 4 × 4 regions) tended to follow sensitivity loss: comparing Figures 3A, 3D with Figures 4A, 4D shows that when per-region sensitivity loss was more severe the correlations with thickness tended to be positive. When the sensitivity loss was less the correlations were not significant. For thinner patches in either eye, the correlations were positive indicating higher sensitivity in thicker regions (see Figs. 4C, 4D). For thicker retinal

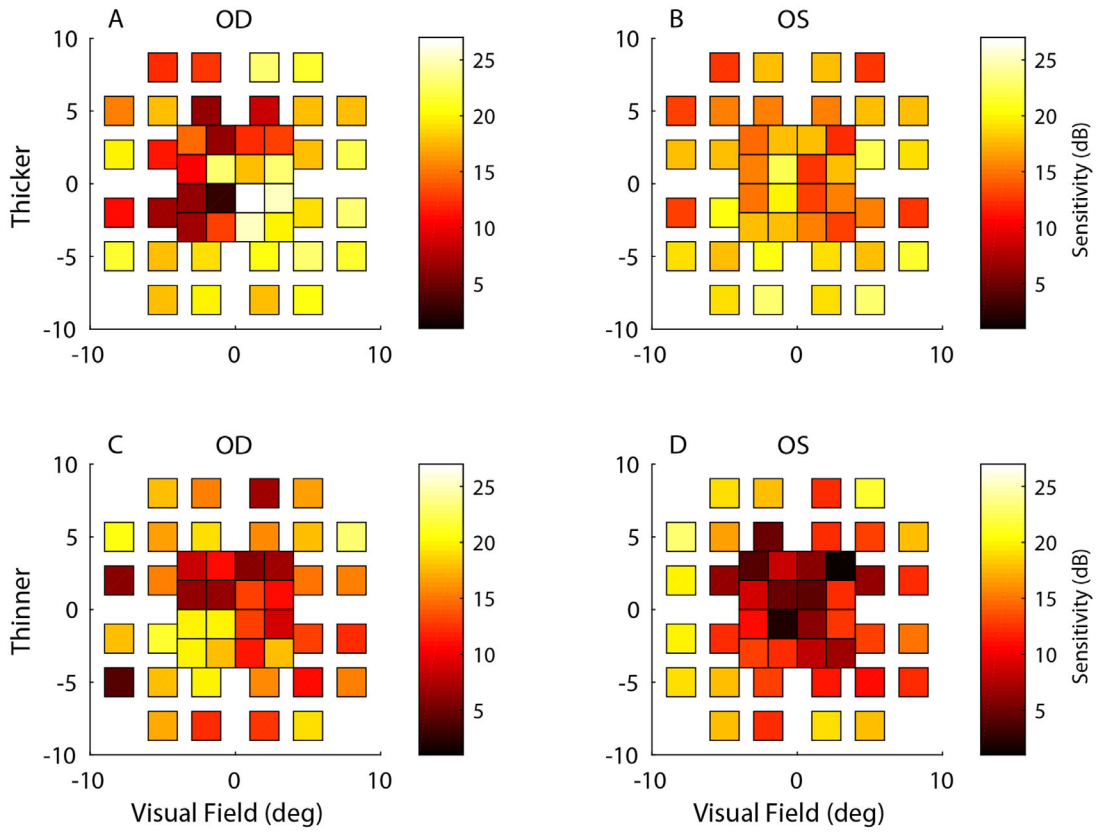

Figure 3. Mean Matrix sensitivity for AMD participants separated into cohorts presenting with (**A, B**) thicker and (**C, D**) thinner retinal patches than the median thickness. That is sensitivity data for each region of each plot were taken from the corresponding regions that contributed to the plots of Fig. 2. Panels **A** and **D** Show deep sensitivity losses centrally confirming that sensitivity loss can be created by retinal thinning or thickening.

presentations, the peripheral correlations were negative, indicating that as thickness became close to normal, sensitivity increased. Counter examples were also present, however.

Table 2 summarizes the correlations among a number of variables, including HCVA, and the means of the 16 inner (8 degrees) and the 28 outer regions of the Matrix sensitivity data and transformed aOCT thickness data (Methods). The P values shown are Bonferroni corrected for the pairs of eyes per subject. There were no significant correlations with LCVA. Seemingly confirming the results from Figure 4 the outer aOCT values were negatively correlated with HCVA ($r = -0.34$, $P = 0.047$), whereas the inner aOCT correlation with HVCA did not reach significance.

We also examined linear mixed-effects models (correcting for multiple comparisons) of our structure/function variables regressed onto HCVA and LCVA. These largely confirmed the correlation analysis of Table 2. For HCVA, the significant independent determinants were: $aOCT_{inner}$, $Sensitivity_{inner}$, and $Sensitivity_{outer}$ (all $P < 0.02$). For LCVA, $aOCT_{inner}$ and $aOCT_{outer}$ were significant ($P < 0.05$).

It seems likely that retinas comprised of many thinner regions are likely to be atrophic, whereas those with thicker values can be trophic. To explore this, we selected the 15 retinas with classic choroidal neovascularization (CNV; see Table 1) and 15 with geographic atrophy ($N = 13$) or sub-retinal fibrosis ($N = 2$). The latter had thinner retinas than average. We then averaged their OCT and Matrix data for inner and outer regions and computed the correlations as for Table 2. The outcomes (Table 3) were very similar to Table 2.

Discussion

In this study, Matrix 10-2 perimetry was used to evaluate the local relationship between retinal sensitivity and thickness at 44 regions across the macula in advanced AMD. We found that macular thickness outside the central eight degrees was more strongly correlated with HCVA than central thickness. Previous studies have reported that mesopic VA is reduced

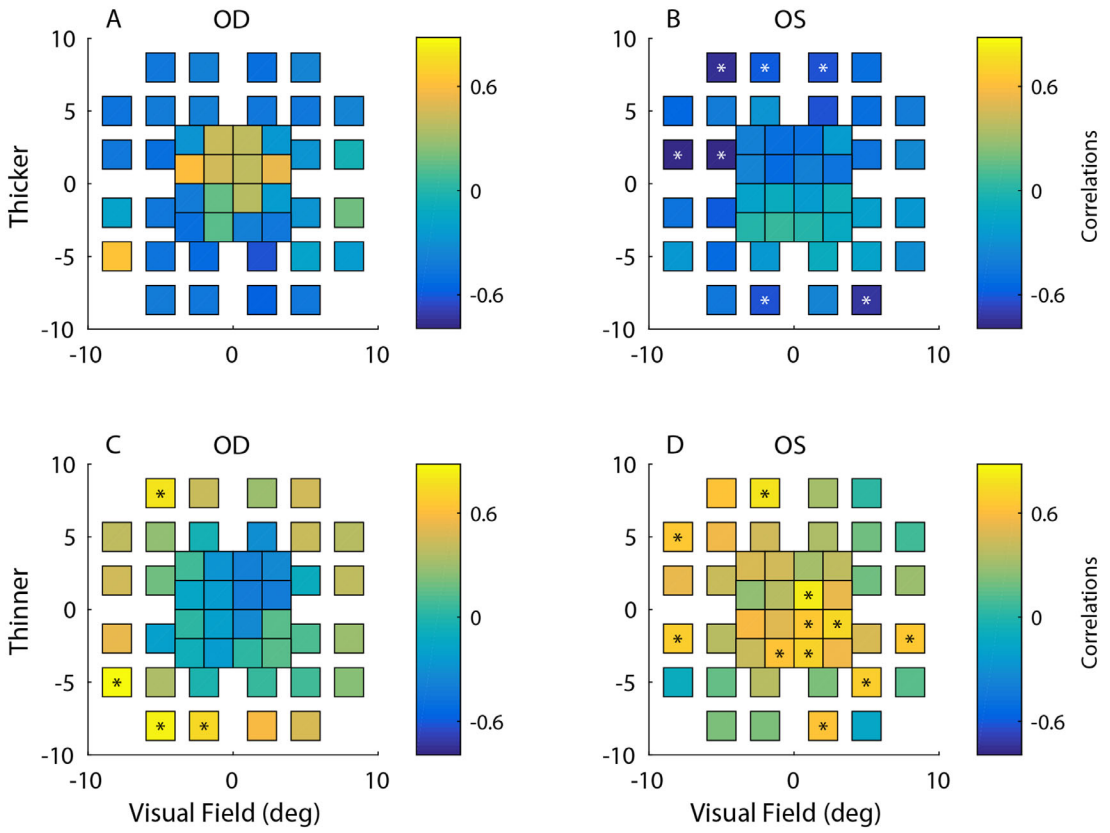

Figure 4. Correlations between Matrix sensitivity and corresponding retinal thicknesses at each region. (**A, B**) Eyes presenting with thicker retinal locations than median value with seven dark blue regions reaching significance for negative correlations with retinal sensitivity. (**C, D**) Eyes presenting with thinner patches showed 15 significant positive correlations (*bright yellow*). The cutoff for significance was very close to ± 0.6 for all regions. The presentation within the central 16 regions tended to follow the sensitivity loss. Outside the central four degrees the results followed retinal thickness. The white or black asterisk (*) indicate significant correlations ($P \leq 0.05$). Correcting for multiple comparisons, 3 correlations in 4B would survive (all outer), 2 in 4C (1 outer), and 4 in 4D (all outer).

Table 2. Correlations Among Changes in Acuity, Thickness, and Perimetric Function

	HCVA	$aOCT_{inner}$	$aOCT_{outer}$
$aOCT_{inner}$	−0.06	1.00	0.58 (<0.001)
$aOCT_{outer}$	−0.34 (0.047)	0.58 (<0.001)	1.00
$Sensitivity_{inner}$	0.73 (<0.001)	−0.24	−0.49 (0.002)
$Sensitivity_{outer}$	0.66 (<0.001)	−0.22	−0.54 (<0.001)

Significant univariate correlations are indicated with a *P* value shown in parentheses (2-tailed, $N = 6$ variables compared, LCVA data not shown as nothing correlated with it). Inner and outer indicate regions inside or outside the central 8 degrees.

Significant associations are shown with a *P* value.

in AMD and is correlated with structural change.[31,32] Here, we made VA measurement more difficult by lowering contrast and did not find significant correlations with structural change. Taken together, these data might suggest that investigating rod function is more promising. New acuity tests using vanishing optotypes may be more effective in AMD.[13] Similarly, retinal sensitivity outside the central eight degrees of the visual field was significantly associated with abnormal central retinal thickness (greater or lesser than normal), but there was no association within the central eight degrees. It has been reported before that although the Matrix and Humphrey 10-2 tests perform similarly in AMD, that neither is well correlated with HCVA.[27]

We found that the correlation between retinal sensitivity and simple thickness was modest, with only one

Table 3. Correlations Among Acuity, Thickness, and Perimetric Function for Trophic and Atrophic Retinas

	HCVA	$aOCT_{inner}$	$aOCT_{outer}$
$aOCT_{inner}$	−0.02	1.00	0.73 (<0.001)
$aOCT_{outer}$	−0.19 (0.047)	0.73 (<0.001)	1.00
$Sensitivity_{inner}$	0.57 (0.002)	−0.34	−0.42 (0.041)
$Sensitivity_{outer}$	0.52 (0.007)	−0.41 (0.051)	−0.58 (0.001)

Significant associations are shown with a *P* value.

peripheral location showing significant correlation (see Figs. 1C, 1D; OD r = 0.42, $P = 0.002$). This is not unexpected given that either pathological thinning or thickening of the retina may cause reduced sensitivity. Indeed, Matrix sensitivity (see Fig. 3) showed deep losses centrally for either thicker or thinner retinas (*cf*. Fig. 3 and Fig. 4) confirming that central retinal thinning or edema may cause sensitivity loss. That has been reported previously for diabetic macular edema.[30] Previous reports in early AMD have found significant correlations between local retinal sensitivity measured with microperimetry and integrity of the inner segment ellipsoid band and retinal pigment epithelial elevation.[33] Our results may represent loss of structural integrity in thinner and thicker retinal regions confirming previous reports of reduced sensitivity in these locations. Our results conclude that retinal thickness at the borders of the macula may potentially predict changes in structure and function nearer fixation, healthier tissue adjacent to the main lesion perhaps reflecting what happens next. Longitudinal studies correlating the structural changes during the evolution of AMD with local retinal sensitivity are required to confirm this.

We found that when we isolated the data by thinner and thicker than normal regions it greatly increased the number of regions showing significant correlations with the Matrix sensitivities. The presentation within the central eight degrees tended to follow the sensitivity loss, when loss was high the correlations with thickness tended to be positive (see Figs. 3A, 3D and Figs. 4A, 4D). When the sensitivity loss was less the correlations were not significant. Outside the central eight degrees, the results followed retinal thickness. For thinner patches in either eye, the correlations indicated that the thinner the retina the lower the sensitivity (*cf*. Figs. 2C, 2D; 3C, 3D; 4C, 4D). For thicker patches, the peripheral correlations were negative, indicating that, as expected, when thickness became close to normal sensitivity went up.

Separating the responses into central and peripheral regions uncovered a novel relationship between structural changes in thickness and function. Evaluating sensitivity at the 16 regions covering the central 8 degrees showed no significant associations with VA but was associated with retinal thickness more peripherally. Interestingly, whereas the outer macular aOCT data was correlated with the inner (and outer) Matrix sensitivity, the inner aOCT was not significantly correlated with the inner Matrix sensitivity (see Table 2). These results reflected the outcomes for HCVA. We found that HCVA was significantly associated with outer retinal thickness and both inner and outer sensitivity. Taken together these outcomes suggest that the outer macular data appear to provide a more consistent marker of eye health than the variable presentation centrally.

Our findings of strong associations between retinal thickness and sensitivity outside the central retina confirms previous reports of an optimal range of retinal thickness that produces peak sensitivity.[30] Hatef and associates[30] failed to find a significant relationship between mean macular sensitivity within the central 12 degrees and BCVA, not dissimilar with our finding for the central 8 degrees. In addition, this result confirms previous findings from our laboratory that responses from regions outside the central retina identifies nAMD eyes that are likely to respond optimally to anti-VEGF therapy.[20] Taken together these findings suggest that there is potential for a novel functional end point other than VA. However, VA remains a critical measure of visual function in clinical studies due to the ease and rapidity of measurement, although alternative measures of macular function may provide a valuable additional information regarding the health of the eye and response to therapy.

Eccentric thickening may influence VA due to the anatomic structure of Henle's layer. Previous studies have evaluated the variability of the foveal shape on retinal thickness in glaucoma to consider the value for customized mapping of the structure and function in the macular area to aid progression analysis. They found hemifield asymmetry in parafoveal shape effecting central retinal thickness measures.[34,35] Our observations of interaction between eccentric thickening in the central eight degrees (2.64 mm) and VA may be influenced by the foveal anatomy of Henle's layer, displacing inner retinal layers in the foveal region.

For example, the displaced foveal ganglion cells could be affected by disease at 2 to 3 mm from the fovea, indirectly affecting VA. A larger sample with varying lesion size would allow us to further explore the relationship between retinal function and thickness.

Several studies have shown that patients with quite severe macular degenerations can have multiple preferred retinal loci[36,37] and may even use them in task specific ways.[38] That being said, these studies tended not to use multiple eccentrically presented fixation aids to augment the centrally presented fixation target as we have done here. That optional feature of the Matrix 10-2 test has been reported in patients with AMD[27] to decrease fixation loss to a median of 0 / 10, as reported here. Although we feel fixation was well-controlled and unlikely to affect our results, there is no doubt that follow-up studies could benefit from measuring the preferred retinal loci (PRL). Another aspect of the Matrix is that the stimuli are 27 times larger in area than standard Goldmann Size 3 stimuli, making the results more robust in the face of small but deep scotomas, which can greatly affect the reproducibility of standard automated perimetry.[39–41] In any case, the possibly more interesting results from a prognostic perspective were for retinal region corresponding to 4 to 10 degrees eccentricity, rather than central regions containing central scotomas.

In summary, this study found a novel relationship among retinal thickness, macular sensitivity, and VA in patients with advanced AMD. We found that retinal thickness in the outer macula was more significantly associated with HCVA and macular sensitivity than central retinal thickness. This highlights the importance for considering the status of the extrafoveal macula as an indicator of VA and retinal function. However, there are limitations to this study that may affect our results. The number of study participants is small and confirming these results in a larger sample is required and also to potentially explore if these findings translate across occult and classic lesions and the various sizes of geographic atrophy. The participants did have their visual capacity assessed in terms of face recognition and quality of life measures.[23,24]

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