Tomoaki Murakami, Naoko Ueda-Arakawa, Kazuaki Nishijima, Akihito Uji, Takahiro Horii, Ken Ogino, and Nagahisa Yoshimura

Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan

Correspondence: Tomoaki Murakami, Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, 54 Shogoin-Kawaracho, Sakyo, Kyoto 606-8507, Japan; mutomo@kuhp.kyoto-u.ac.jp.
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PURPOSE. To integrate parameters on spectral-domain optical coherence tomography (SD-OCT) in diabetic retinopathy (DR) based on the self-organizing map and objectively describe the macular morphologic patterns.

METHODS. A total of 336 consecutive eyes of 216 patients with DR for whom clear SD-OCT images were available were retrospectively reviewed. Eleven OCT parameters and the logarithm of the minimal angle of resolution (logMAR) were measured. These multidimensional data were analyzed based on the self-organizing map on which similar cases were near each other according to the degree of their similarities, followed by the objective clustering.

RESULTS. Self-organizing maps indicated that eyes with greater retinal thickness in the central subfield had greater thicknesses in the superior and temporal subfields. Eyes with foveal serous retinal detachment (SRD) had greater thickness in the nasal or inferior subfield. Eyes with foveal cystoid spaces were arranged to the left upper corner on the two-dimensional map; eyes with foveal SRD to the left lower corner; eyes with thickened retinal parenchyma to the lower area. The following objective clustering demonstrated the unsupervised pattern recognition of macular morphologies in diabetic macular edema (DME) as well as the higher-resolution discrimination of DME per se. Multiple regression analyses showed better association of logMAR with retinal thickness in the inferior subfield in eyes with SRD and with external limiting membrane disruption in eyes with foveal cystoid spaces or thickened retinal parenchyma.

CONCLUSIONS. The self-organizing map facilitates integrative understanding of the macular morphologic patterns and the structural/functional relationship in DR.

Keywords: diabetic retinopathy, diabetic macular edema, optical coherence tomography, self-organizing map

Diabetic retinopathy (DR) is a leading cause of severe visual loss worldwide, and especially diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR) often result in visual disturbances. Although several therapeutic strategies have been developed for DME, including photocoagulation, steroids, anti-VEGF drugs, and vitrectomy, DME is often refractory to treatment and has a poor visual prognosis. Diabetes disrupts the blood-retinal barrier (BRB) in the retinal vasculature, leading to edematous changes in the neuroglial tissue in the macula and concomitant visual loss.

DME previously has been diagnosed subjectively as macular thickening seen on biomicroscopy, color fundus photography, and fluorescein angiography (FA) images in the Early Treatment Diabetic Retinopathy Study (ETDRS). In contrast, optical coherence tomography (OCT) enables objective measurement of the macular thickness, and the Diabetic Retinopathy Clinical Research Network (DRCRnet) has proposed center-involved DME, depending on the averaged macular thickness determined by OCT. The DRCRnet further reported a modest correlation between the macular thickness and visual acuity (VA) in DME, suggesting the clinical relevance of the macular thickness on OCT as well as other mechanisms causing visual disturbances, including ischemia and neuroglial degeneration in the macula. OCT also provides qualitative information about macular pathomorphologies, including cystoid macular edema, serous retinal detachment (SRD), and spongelike retinal swelling. Recent advances in OCT technology are providing better delineation of the fine physiologic and pathologic structures and are encouraging clinicians to investigate the association between the VA and foveal photoreceptor damage represented by the external limiting membrane (ELM) and the junction between the inner and outer segments (IS/OS) in DME.

The pathology in the vitreomacular interface or hyperreflective foci also have been seen on OCT images and have clinical relevance in DME.

The increasing number of OCT parameters has made models for classification or prediction more complex, and clinicians cannot integratively understand DME based on the OCT images. A self-organizing map, one of the artificial neural network algorithms, produces low-dimensional topology-preserving representations of the high-dimensional input data. Unsupervised machine learning by this algorithm can show a two-dimensional lattice map on which mathematical similarity between nodes was represented by the geographic distances. Concomitantly, the subsequent clustering is one of the heuristic methods that suggest the novel classifications or segmentation in the multidimensional data. Recent medical and biologic advances often provide high-throughput data with too many
parameters that are visualized and simply understood after application of self-organizing map. Makinen et al. reported an association between metabolic phenotypes and vascular complications in type 1 diabetes, based on the self-organizing map. The Encyclopedia of DNA Elements Project also applied the self-organizing map to the human genome informatics to interpret gene expression profiles. These reports successfully discovered novel knowledge by using this unsupervised machine learning with clustering. However, it remains to be evaluated how the self-organizing map demonstrates the macular morphologic patterns described by multidimensional OCT parameters in DME.

In the current study, the self-organizing map enabled us to integrate multiple OCT findings onto two-dimensional maps to visualize the local associations and dissociations between the individual parameters and to objectively classify all 336 eyes of patients with DR into five macular morphologic patterns.

**METHODS**

**Patients**

A total of 336 eyes of 216 patients with DR (115 men, 101 women; mean age, 64.3 ± 11.6 years; range, 23–89 years) were studied retrospectively at the Department of Ophthalmology in Kyoto University Hospital from November 2007 to April 2011. Four patients had type 1 diabetes, and 212 patients had type 2 diabetes; eight eyes had mild nonproliferative diabetic retinopathy (NPDR), 122 eyes moderate NPDR, 105 eyes severe NPDR, and 101 eyes PDR. They were often accompanied with DME and/or the lesions at the vitreoretinal interface, including epiretinal membrane and vitreomacular traction. Eyes that had not been treated for DME and for which OCT images of sufficiently good quality were available were consecutively included. Resultantly, eyes with tractional retinal detachment involving the macula or vitreous hemorrhage had poorer image quality, and were not included in this study. The main exclusion criteria were other chorioretinal diseases and ocular diseases affecting visual function other than pathological macular changes regarding DR. The research and measurements adhered to the tenets of the Declaration of Helsinki; the ethics committee of our institution approved the study.

**Quantification of OCT Parameters**

After fundus biomicroscopy and measurement of the best-corrected VA, retinal sectional imaging using Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) was performed in the standard manner. Briefly, we set and maintained a constant distance from the iris to the front lens of this instrument, and then brought the retina on the infrared images into focus using the focus knob, which was synchronized with the measurement of the refractive error in this instrument. The corneal curvature radii and the refractive error in individual eyes and other parameters in Gullstrand’s schematic eye were applied to calculate the focal length in the Heidelberg Eye Explorer software. The trigonometric function of the focal length in each eye and the visual angles of the scans enable the software to calculate the corrected transverse length on the retina in each eye, comparing to the standard data in the schematic eye.

For quantitative analysis of OCT images, 20-degree radial scans centered on the fovea were obtained in a clockwise manner, and 49 raster scans were used to evaluate the mean retinal thickness from the internal limiting membrane (ILM) to the RPE at the fovea (radius, 500 μm) and in four subfields (superior, nasal, inferior, and temporal) in the parafoveal areas (radius, 500–1500 μm), according to the manufacturer’s protocol.

We measured the height of the cystoid spaces or SRD at the presumed foveal center. Briefly, the presumed foveal center where the inner layers from the ILM to the inner nuclear layer (INL) are absent was determined as described previously, followed by measurement of the height of the cystoid spaces (from the innermost to the outermost lumen) or the SRD (from the outer segment to the surface of the RPE). We also evaluated the thickness of the retinal parenchyma at the fovea by subtracting the height of the cystoid spaces or SRD from the total retinal thickness at the fovea. Another parameter to evaluate the foveal photoreceptor status is the percentage of ELM disruption at the fovea, as previously described.

We also determined the degree of the cystoid spaces in either the INL or outer plexiform layer (OPL) in the parafoveal areas, as described recently. Briefly, we evaluated the retinal cystic changes horizontally 500 μm from the presumed foveal center at each clock hour in radial sections and scored them from 0 (absent at any clock hour) to 12 (present at all clock hours).

**Self-Organizing Map**

Twelve parameters (retinal thicknesses in the central subfield and the parafoveal subfields [superior, inferior, nasal, and temporal] of ETDRS grid, the height of cystoid spaces or SRD at the fovea; the thickness of retinal parenchyma; the ELM status at the fovea; degrees of cystoid spaces in INL or OPL in the parafovea; and the logarithm of the minimal angle of resolution [logMAR] VA) were analyzed using the batch-learning self-organizing map algorithm (Viscovery SOMine; Euadaptics Software GmbH, Vienna, Austria), which maps multidimensional data onto two-dimensional maps with topology preservation, and enables us to, unsupervised, recognize the macular morphological patterns in eyes with DR.

The self-organizing map is an artificial neural network algorithm that has two layers (i.e., the input layer and the competitive layer) for unsupervised machine learning. Briefly, all parameters in the reference vectors were normalized to the same levels (between 0 and 1) so as to avoid the biases by the absolute values in some parameters. After all the reference vectors were input at the same time in parallel, the distance between the reference vector in the input layer and the weight vector of the nodes in the competitive layer were calculated. Then the best matching unit (node) in the competitive layer, which is the nearest to the reference vector, was determined for any reference vector. Each weight vector of the best matching unit and their neighbors were made similar to the reference vectors according the neighborhood. The processes of this competitive machine learning were repeated a sufficient number of times, with a resultant map in which eyes were arranged close to each other according to the degree of their similarities; eyes with different profiles were farther away. In other words, the mathematical distances between eyes with multidimensional data were converted to the geographical distances on a two-dimensional lattice map.

In addition, eyes with the multidimensional data were clustered objectively by the SOM-Ward method by using the Viscovery SOMine software. The multidimensional dataset was analyzed using the self-organizing map algorithm, followed by Ward’s method, one of the most common agglomerative cluster analyses. Briefly, the SOM-Ward method started with clusters containing each single node. In each step, the distances between the clusters were defined as the differences between the error sum of squares (the sum of squared Euclidian distance between any node and the centroid) in
the two clusters and that in the merged cluster. Two clusters with a minimal distance between them were merged into one single cluster. The agglomerative procedures were repeated until all nodes were within one cluster. The software then computed the cluster indicator for each cluster count according to the intercluster distances and the number of clusters in each step and concomitantly selected the clustering with minimal variance, which would be better for objective segmentation or pattern recognition.

To validate the map with the absolute values in retinal thicknesses, we then used the self-organizing map algorithm and the percentage changes in the retinal thicknesses. Comparing with the normative data, the percentage changes in the retinal thicknesses were calculated in five subfields of the ETDRS grid, according to the formula shown below.\(^{36}\)

\[
\text{Percentage change (\%)} = \frac{(\text{thickness in each eye}) - (\text{thickness in the normative data})}{\text{(thickness in the normative data)}} \times 100
\]

Twelve parameters containing the percentage changes in the retinal thicknesses of five subfields and another seven parameters were applied to the algorithm in the same setting.

### Statistical Methods

Analysis of variance was used to compare quantitative data populations with normal distributions and equal variance. The data were analyzed using the Kruskal-Wallis test for populations with nonnormal distributions or unequal variance. Linear regression analysis was performed to test the statistical significance of the correlations.

### Table 1: Association Between logMAR VA and Various Parameters on OCT Images in DR

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Correlation With logMAR VA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central subfield thickness</td>
<td>( R = 0.529, P &lt; 0.001 )</td>
</tr>
<tr>
<td>Superior subfield thickness</td>
<td>( R = 0.498, P &lt; 0.001 )</td>
</tr>
<tr>
<td>Temporal subfield thickness</td>
<td>( R = 0.505, P &lt; 0.001 )</td>
</tr>
<tr>
<td>Inferior subfield thickness</td>
<td>( R = 0.481, P &lt; 0.001 )</td>
</tr>
<tr>
<td>Nasal subfield thickness</td>
<td>( R = 0.465, P &lt; 0.001 )</td>
</tr>
<tr>
<td>Foveal cystoid spaces height</td>
<td>( R = 0.379, P &lt; 0.001 )</td>
</tr>
<tr>
<td>Foveal SRD height</td>
<td>( R = 0.285, P &lt; 0.001 )</td>
</tr>
<tr>
<td>Retinal parenchyma thickness</td>
<td>( R = 0.020, P = 0.721 )</td>
</tr>
<tr>
<td>Degree in cystoid spaces in INL</td>
<td>( R = 0.412, P &lt; 0.001 )</td>
</tr>
<tr>
<td>Degree in cystoid spaces in OPL</td>
<td>( R = 0.423, P &lt; 0.001 )</td>
</tr>
<tr>
<td>ELM disruption at the fovea, %</td>
<td>( R = 0.581, P &lt; 0.001 )</td>
</tr>
<tr>
<td></td>
<td>Superior Thickness</td>
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<tr>
<td>----------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Central thickness</td>
<td>$R = 0.842, P &lt; 0.001$</td>
</tr>
<tr>
<td>Superior thickness</td>
<td>$R = 0.807, P &lt; 0.001$</td>
</tr>
<tr>
<td>Temporal thickness</td>
<td>—</td>
</tr>
<tr>
<td>Inferior thickness</td>
<td>—</td>
</tr>
<tr>
<td>Nasal thickness</td>
<td>—</td>
</tr>
<tr>
<td>Cyst height</td>
<td>—</td>
</tr>
<tr>
<td>SRD height</td>
<td>—</td>
</tr>
<tr>
<td>Retinal parenchyma</td>
<td>—</td>
</tr>
<tr>
<td>Cysts in INL</td>
<td>—</td>
</tr>
<tr>
<td>Cysts in OPL</td>
<td>—</td>
</tr>
</tbody>
</table>

Central thickness, thickness of central subfield; cyst height, height of foveal cystoid spaces; cysts in INL, degree of cystoid spaces in INL; cysts in OPL, degree of cystoid spaces in OPL; ELM disruption, ELM disruption at the fovea (%); inferior thickness, thickness of inferior subfield; nasal thickness, thickness of nasal subfield; retinal parenchyma, thickness of retinal parenchyma; SRD height, height of foveal SRD; superior thickness, thickness of superior subfield; temporal thickness, thickness of temporal subfield.
correlation. After eliminating the confounding factors, multiple linear regression analysis with a stepwise forward approach was performed to identify the model for predicting logMAR VA. A \( P \) less than 0.05 was considered statistically significant.

RESULTS

Multiple OCT Parameters in DR

OCT initially was used to quantify the retinal thickness in various macular diseases, including DME. The macular thickness was correlated modestly with visual function in DME (Table 1), suggesting the clinical relevance of the macular thickness as well as the presence of unknown pathogeneces. Recent advances in OCT technology have improved the image resolution with reduced speckle noises to enable measurement of additional parameters in DME. It seems that multiple findings and parameters should define the pathogenesis more precisely, although the dimensionality (or concentration of measure) often has caused confusion in the interpretation of the multidimensional data (Table 2).

Visualization of Multidimensional Data in DR Based on Self-Organizing Map

In the current study, we applied the self-organizing map algorithm to multiple OCT parameters (Fig. 1) and visualized the relationships and patterns between individual parameters. Retinal thickening in the superior subfield was most significant on the left side of the map, which is similar to that in the temporal subfield. The cases with a thicker retina in the nasal subfield and those with thickening in the inferior subfield were distributed in the lower-left corner of the map, which was supported by the significance of the correlation (Table 2). The eyes with higher foveal cystoid spaces were grouped with those with more cystoid spaces in the INL or OPL in the upper-left corner of the map (Fig. 1). The cases with a disrupted ELM were to some extent colocalized with those with poor logMAR VA in the upper-left corner, lower-left corner, and upper area of the map (Fig. 1).

Eyes with higher foveal cystoid spaces did not have higher foveal SRD or thickened retinal parenchyma at the fovea in the map (Fig. 1). Eyes with higher foveal SRD were also not accompanied by greater cystoid spaces or thickened retinal parenchyma at the fovea. In addition to these exclusive relationships, eyes with cystoid spaces or SRD at the fovea (left side of the map), but not eyes with thickened retinal parenchyma (lower side of the map), were colocalized with those with a thicker superior or temporal subfield in the parafoveal area (Fig. 1). We also used this algorithm with the percentage changes in the retinal thicknesses and confirmed the similar results regarding the macular morphological patterns (Fig. 2).
Macular Morphologic Patterns in DR

These local relationships suggested the presence of patterns in these parameters, which encouraged us to analyze this self-organizing map using additional clustering by Ward's method. All eyes were divided into five segments (Figs. 3A, 4).

The combination of the visualized patterns on the two-dimensional map and statistical analyses between segments showed several characteristics in the individual segments (Figs. 4, 5). Segment 1 included eyes with almost normal thicknesses in any subfield, regardless of whether the ELM was intact or disrupted. Segment 2 included eyes with mild foveal thickening, smaller cystoid spaces or SRD at the fovea, and better VA. Segment 3 included eyes with thickened retinal parenchyma at the fovea but no cystoid spaces or SRD at the fovea, and better VA.

Segment 4 or 5 included eyes with higher cystoid spaces or SRD at the fovea, respectively. These data suggested that macular thickening in DME results at least partly from several patterns of pathogeneases.

We then re-plotted each case on the graph that showed a modest correlation between macular thickness and logMAR VA in DR (Fig. 3B). We found trends in the location in each subgroup on the graph, although the borders between the individual segments were not definite.

We investigated the relationship between DR severity and the macular morphologic patterns (Table 3). Fifty-seven (54.3%) of 105 eyes with severe NPDR were in segments 2 to 5 and seemed to have DME more frequently than those with moderate NPDR or PDR (36.1% or 35.6%). Ten (9.5%) or 21 (20.0%) eyes with severe NPDR especially had high cystoid spaces or SRD at the fovea (segment 4 or 5), compared with those with moderate NPDR (2.5% or 4.9%, respectively).

 Associations Between Visual Function and OCT Characteristics

We used multiple regression analyses in all 336 eyes and found that the logMAR VA was correlated with the retinal thickness in the central subfield and ELM disruption at the fovea (R = 0.337, P < 0.001 and R = 0.451, P < 0.001, respectively). Compared with the heterogeneity in all eyes in this study, eyes in individual segments had relatively homogeneous characteristics, which prompted us to apply multiple regression analyses in each segment. The logMAR VA was correlated with ELM...
disruption at the fovea in eyes in segments 3 and 4, and there was a significant association between the logMAR VA and the retinal thickness in the inferior subfield in eyes in segment 5 (Table 4).

**DISCUSSION**

Recent advances in OCT technology allow measurement of the increasing number of morphologic parameters in DME, which should promote a better understanding of its pathogenesis and clinical profiles. However, the higher dimension of the data has been a definite barrier to establishing disease models, which Bellman mathematically documented as “the curse of dimensionality.” In the current study, individual cases with multiple parameters on OCT images with preserved topology were simply visualized and arranged in a two-dimensional space based on the self-organizing map algorithm (Fig. 6), although the array of hexagons in the map was the particular view of this software (Viscovery SOMine; Eudaptics Software GmbH) and alternative ways might improve the data visualization. We discovered novel associations and dissociations between individual parameters in subpopulations. The subsequent clustering further provided the high-resolution segmentation of macular pathomorphologies in DME. Although we confirmed the reproducibility using the datasets with absolute values or percentage changes in retinal thicknesses, further independent studies should be planned.

DME was clinically diagnosed as macular thickening in eyes with DR, although a definitive diagnosis is often difficult because of the diversity of its pathogenesis and clinical findings seen on biomicroscopy, FA, and OCT. Generally, vascular hyperpermeability is believed to increase the volume of the extracellular spaces and concomitant macular thickening, with a diversity of the morphologies, in the pathogenesis of DME. These issues suggested the need for better clinical criteria for therapeutic strategies against DME. Previously, the ETDRS defined DME that required photocoagulation as clinically significant macular edema, depending on the findings in fundus microscopy and FA, and DRCRnet recently reported center-involved DME, determined by OCT measurements, as requiring intervention. In addition to these clinical diagnoses, the clustering combined with the self-organizing map in the current study might objectively provide high-resolution discrimination that eyes without DME were classified into segment 1, whereas those with DME were classified into segments 2 to 5. It would be more relevant for clinicians if the objective diagnosis of DME or the classification of morphological patterns in DME was supported by multiple parameters rather than only one parameter.

In the current study, the clustering further visualized the high-resolution segmentation of eyes with DME according to the patterns of macular morphology (segments 2–5). Segments 3, 4, and 5 might to some extent correspond to spongelike retinal swelling, cystoid macular edema, and SRD, respectively.
as reported previously.\textsuperscript{19} Recent publications also have shown that perifoveal hyperfluorescence is related to foveal SRD and that eyes with foveal cystoid spaces often have an enlarged foveal avascular zone or microaneurysms.\textsuperscript{35,39} Taken together, different pathogeneses in vascular lesions might lead to the different patterns of macular morphologies, which was confirmed by the objective clustering with the SOM-Ward method.

We evaluated the relationship between DR severity and the patterns of macular morphologies, and showed that the distributions of eyes in individual segments differed among the severity categories of DR. This suggested that the macular morphological patterns might be clinically useful for predicting the severity of DR to some extent. Future studies are needed to determine whether this approach using fundus findings is useful for classifying the severity of DR. In addition, the macular morphologies might depend on the pathogenesis regarding the severity of DR. In particular, eyes with severe NPDR had DME (corresponding to segments 2–5) more frequently than those with moderate NPDR. These data might be compatible with that the severe BRB disruption can be represented by multiple retinal hemorrhages, one of the definitions of severe NPDR.

If we focus only on foveal cystoid spaces, it is strange that segment 2 was differentiated from segment 4. The major characteristics of segment 4 were a higher degree of parafoveal cystoid spaces in the INL or OPL, higher foveal cystoid spaces, more severe disruption of ELM, and the poorest VA, compared with those of segment 2 (Fig. 5). It was reported that the remodeling in the perifoveal capillary networks is associated with foveal cystoid spaces in DME,\textsuperscript{35} and that the parafoveal edematous changes were correlated with visual disturbance in eyes with intact ELM at the fovea.\textsuperscript{20} Taken together, the parameters in segment 2 suggested minimal changes at the fovea with better vision, whereas both light perception at the fovea and the transmission system by secondary or tertiary neurons caused severe visual impairments in eyes in segment 4.

Many studies have reported a modest correlation between the macular thickness and VA in DME.\textsuperscript{18} It is reasonable that macular ischemia or neuroglial degeneration results in visual disruption without macular thickening,\textsuperscript{20–25,40} and these

| Table 3. Relationship Between Macular Morphological Patterns and DR Severity |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Segment 1                       | Mild NPDR       | Moderate NPDR   | Severe NPDR     | PDR             |
|                                 | 5               | 78              | 48              | 65              |
| Segment 2                       | 1               | 22              | 16              | 9               |
| Segment 3                       | 0               | 13              | 10              | 9               |
| Segment 4                       | 0               | 3               | 10              | 10              |
| Segment 5                       | 2               | 6               | 21              | 8               |

Values are number of eyes.

<table>
<thead>
<tr>
<th>Table 4. Multiple Regression Analysis of Each Segment in DR</th>
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<tbody>
<tr>
<td>Segment</td>
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<tr>
<td>1</td>
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<td>2</td>
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<tr>
<td>4</td>
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<tr>
<td>5</td>
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</table>
outliers would negate the statistical significance. In the current study, the eyes in segment 1 had better VA and thinner retinas, whereas the eyes in segments 4 and 5 had poor VA with thicker retinas. The eyes in segments 2 and 3 characteristically were between segments 1 and 4 (or 5) regarding the central thickness; in other words, a modest correlation between central thickness and visual function could be explained by combining those subpopulations (Fig. 3B). In addition, we could not definitively discriminate between these segments in Figure 3B; the border on the self-organizing map was clear (Fig. 4), whereas the meaning of the x- and y-axes on the map was lost.

The results of regression analyses improved after the clustering divided all 336 eyes into five homogeneous subgroups. In particular, we saw a better correlation between the logMAR VA and ELM disruption, which represented the damaged photoreceptors, in the eyes in segments 3 and 4. We thus speculated that the impact of the damaged photoreceptors at the fovea was more severe than that of the edematous changes in the transmission system in the parafovea in the eyes in segment 4. Most eyes (78.1%) in segment 3 had epiretinal membrane or vitreomacular traction, although the photoreceptor damage at the fovea contributed more to visual disturbances. Further, the significant correlation in segment 5 might allow us to hypothesize that subretinal fluids can migrate inferiorly because of gravity, and, as a result, the thickness in the inferior subfield best represented the magnitude of the SRD. In contrast, the parameters that are associated with the logMAR VA in the eyes in segment 2 need to be investigated.

The current study evaluated for the first time multiple parameters on SD-OCT images based on the self-organizing map and provided a novel and integrative understanding of the macular morphologic patterns in DME, which may shed light on the path to customized medicine.

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**Figure 6.** Hexagonal units corresponding to three typical cases of DME. The characteristics of the macular morphology in the individual cases are easily and integratively understood in comparison with the trends in all cases.
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