SPECTRALIS Optical Coherence Tomography Angiography (OCTA): Principles and Clinical Applications

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ABSTRACT

Optical coherence tomography angiography (OCTA) is a technique to visualize vascular perfusion in the retina and choroid without dye injection. Various commercial implementations of OCTA have been introduced for use in clinical practice, each with specific attributes, functions, strengths, and limitations. This paper provides a comprehensive overview of the design principles of Heidelberg Engineering's SPECTRALIS OCTA Module, which is part of the SPECTRALIS multimodal imaging platform. Clinical examples are shown to illustrate the diagnostic applicability of the SPECTRALIS OCTA Module while highlighting its unique features and demonstrating its clinically relevant capabilities.

Key Words: *Retina; Optical coherence tomography; OCT angiography; OCTA; SPECTRALIS; Heidelberg Engineering*

BACKGROUND

Optical coherence tomography angiography (OCTA) is a non-invasive imaging technique that provides three-dimensional visualization of perfused vasculature of the retina and choroid. In contrast to standard structural OCT, OCTA analyzes not only the intensity of the reflected light but also the temporal changes in the reflection caused by moving particles, such as erythrocytes flowing through vessels. These changes in the OCT signal are detected by repeatedly capturing OCT images at each point on the retina and allowing for the creation of image contrast between perfused vessels and static surrounding tissues; see **Figure 1**. To acquire such data, various algorithms have been established by several manufacturers, making resultant images different in appearance from one another.[1] Such variances in each device's output may result in different clinical diagnostic interpretations.

The performance of each device's OCTA algorithm is dependent on specific acquisition protocols that have been tailored to offer optimal information required for an indication. More specifically, the success of an algorithm may be dependent on the number of repeated OCT scans at each retinal location, and the sensitivity of the algorithm to differentiate particles in motion from static tissue. In addition to these considerations, each device may also differ with regards to acquisition speed and the retinal boundaries that are applied to differentiate various vascular plexuses (using *en face* images generated from slabs).

Moreover, while each unique OCTA algorithm is subject to slightly different limitations that are attributed to its overall approach, there are certain confounding factors and/or limitations that impact all algorithms and are innate characteristics of this imaging modality. These factors include, but are not limited to, reduced light penetration in deeper layers and image artifacts projected from more superficial layers to deeper ones.

It is important to understand and acknowledge each device's OCTA capabilities in order to ensure optimal use of the technology in a clinical setting. Therefore, this paper aims to provide insight into the principles and the clinical application of the SPECTRALIS OCTA Module.

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PRINCIPLES

Acquisition and Retinal Tracking

The core principle of OCTA is the detection of OCT signal changes over time, caused by intravascular motion of blood cells. These changes are acquired and assessed via repeated acquisitions of OCT images at the same location. When assessing such changes in images of an eye, it is important to consider that ocular movements during acquisition contribute to bulk motion in the images. Such movements cause the OCT signal of static tissue to change gradually over time (eye drift) or abruptly (saccades), thereby introducing signal changes that need to be considered and corrected. In instances where bulk motion is small enough (eye drift) so that there is sufficient spatial overlap of consecutive OCT images, the resulting OCT signal changes within the static tissue can be corrected by image processing, such as image registration;[1] see **Figure 1**. In instances of abrupt eye movements (i.e. saccades or eye blinks, which are likely to occur during the acquisition of volume scans on any commercial OCTA device), image processing techniques alone cannot compensate for bulk motion. This is because bulk motion correction via image processing requires spatial overlap of successive OCT images, which cannot be guaranteed in the event of strong eye movements. With abrupt eye movements, the actual scanning path of the OCT laser beam deviates from the nominal scanning path. This deviation of the scanning path leads to geometrical distortions and missing data in the OCTA volume scans.

If the scanning path of the OCT laser beam is not actively monitored and controlled during acquisition, it is likely that OCTA volume scans are subjected to geo-metrical distortions and/or missing data.

Some devices attempt to correct for such distortions by combining information from several OCTA volume scans, after image acquisition (i.e. by post-processing techniques).[2,3] The images derived from such approaches seem to be accurate and without motion artifacts upon initial inspection. However, without direct comparison to ground-truth images (i.e. histology or dye-based angiography), it is difficult to confirm whether these images represent the true anatomy of eye structures imaged. It is critical to ensure that any observed change in vasculature is due to true temporal physiological changes rather than due to geometrical distortions. Geometrical distortion correction by post-processing introduces side effects of interpolation, such as reduced or inhomogeneous spatial resolution.[4] If OCTA data is not acquired equidistantly across the retina and is subject to interpolation, small vasculature such as capillaries may not be captured correctly.

The SPECTRALIS TruTrack Active Eye Tracking technology corrects for displacements by reacquisition of OCT images at the correct retinal location in real-time. The eye movements are measured using confocal scanning laser ophthalmoscope (cSLO) images, and these measurements are used to precisely re-position each individual OCT scan within a volume. This eye tracking approach diminishes the introduction of geometrical distortions and missing data, ensuring that the data acquired from visit to visit is devoid of errors that may reduce the precision of quantitative change analyses. Extensive post-processing such as recombination of OCTA volume scans by orthogonal scan registration is avoided.[2,3,5,6] The real-time data filtration contributes to longer

SPECTRALIS OCTA acquisition times relative to other techniques that do not account for such motion artifacts during scan acquisition. However, if eye tracking does not effectively correct for eye movements in real-time, it is more likely that the true anatomy of eye structures is misrepresented in the final volumetric data.

OCTA Algorithm

In order to identify temporal changes in the OCT signal associated with blood flow, several OCT images are acquired at the same retinal location in short succession. If static tissue is imaged with precise tracking, the OCT signal changes gradually over time. Bulk motion correction can correct for such changes induced within static tissue, yielding spatially aligned images. This image alignment will not suppress the temporal changes observed at locations with perfused blood vessels.

Therefore, assessment of the difference in OCT signal between aligned OCT images allows for identification of pixels in which larger changes over time were caused by moving blood cells within perfused blood vessels (flow); see **Figure 1 C**. Considering the physiological flow speeds of perfused ocular vasculature and the typical time intervals of several milliseconds between consecutive OCT images, it is very unlikely to observe the same blood cells in two successive images. As a result, the OCT signal from within perfused vasculature varies randomly with time and the variation is much greater than the residual changes induced by measurement noise from static tissue.

The current commercially available OCTA devices use different algorithms to detect these larger temporal variations in OCT signal that are associated with blood flow. OCTA algorithms vary in their ability to create contrast between static tissue and flow.[1]

Some of the currently available OCTA algorithms only consider that the temporal variations in OCT signal induced by static tissue and by perfused vasculature are simply different. These algorithms do not sufficiently account for the expected high variability of signal intensities in static tissue and for how the temporal changes of these intensities differ from changes induced by flow. Therefore, the outputs of these algorithms have a biased correlation to OCT signal intensity and provide non-zero values for static tissue compo-
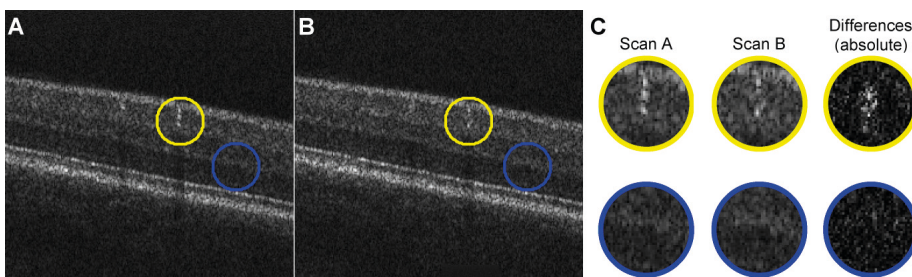

Figure 1: Example of how the OCT signal intensity changes over time, after bulk motion correction. A, B: Structural OCT images were acquired with a time difference of 8 milliseconds. The location of a larger blood vessel (yellow circle) and of static tissue (blue circle) is indicated in both images. C: Upon magnification of these areas and calculation of the differences, larger OCT signal changes can be seen within the blood vessel when compared with the static tissue. Note that this figure is not showing the SPECTRALIS OCTA algorithm results, but just the absolute differences between two single OCT scans (A and B) for illustration.

nents. This results in OCTA images with reduced contrast.

The SPECTRALIS OCTA algorithm is based on a different approach. The temporal changes of the OCT signal within static tissue and those within perfused vasculature follow two distinct distributions which can be derived from theory and observation (including sources of measurement noise). Given these distributions and a short time-series of samples (from 4 to 7 repeated scans), it is possible to determine the probability of whether the signal at that sample location (i.e. a pixel in a B-scan) corresponds to one of the two distributions. The SPECTRALIS OCTA algorithm is based on such a probabilistic approach. The algorithm computes the probability that a given pixel follows the OCT signal distribution of perfused vasculature (flow) rather than the distribution of static tissue. For this reason, SPECTRALIS OCTA images have an almost binary, high-contrast appearance. Increasing the number of repeated scans at each location increases the certainty of the algorithm and, therefore, the contrast between perfused vessels and static tissue. High quality OCTA images can be obtained using 4 repeated scans, but the contrast can be further increased by acquiring up to 7 repeated scans.

The SPECTRALIS OCTA algorithm is a full-spectrum probabilistic approach: it provides OCTA volume scans without sacrificing resolution in any spatial dimension. This is in contrast to approaches that sacrifice resolution for noise reduction, such as split-spectrum amplitude-decorrelation angiography.[7] The SPECTRALIS OCTA does not apply spatial filtering and, therefore, the OCTA data represents the raw output of the algorithm at the original resolution (i.e. 5.7 µm to 11.4 µm laterally and 3.9 µm in depth). Additional filtering techniques, such as noise reduction by spatial averaging, have not been implemented during acquisition because filtering (e.g. with a vessel-shaping Frangi filter[8]) can easily introduce artifacts that are hard to discern from real vascular structures, and may reduce the resolution and/or image contrast. Although the unfiltered SPECTRALIS OCTA images tend to be noisier than highly filtered images from other OCTA devices, image interpretation is not hindered by the noise as it is easy to visually discriminate noise from signal via dynamic review.
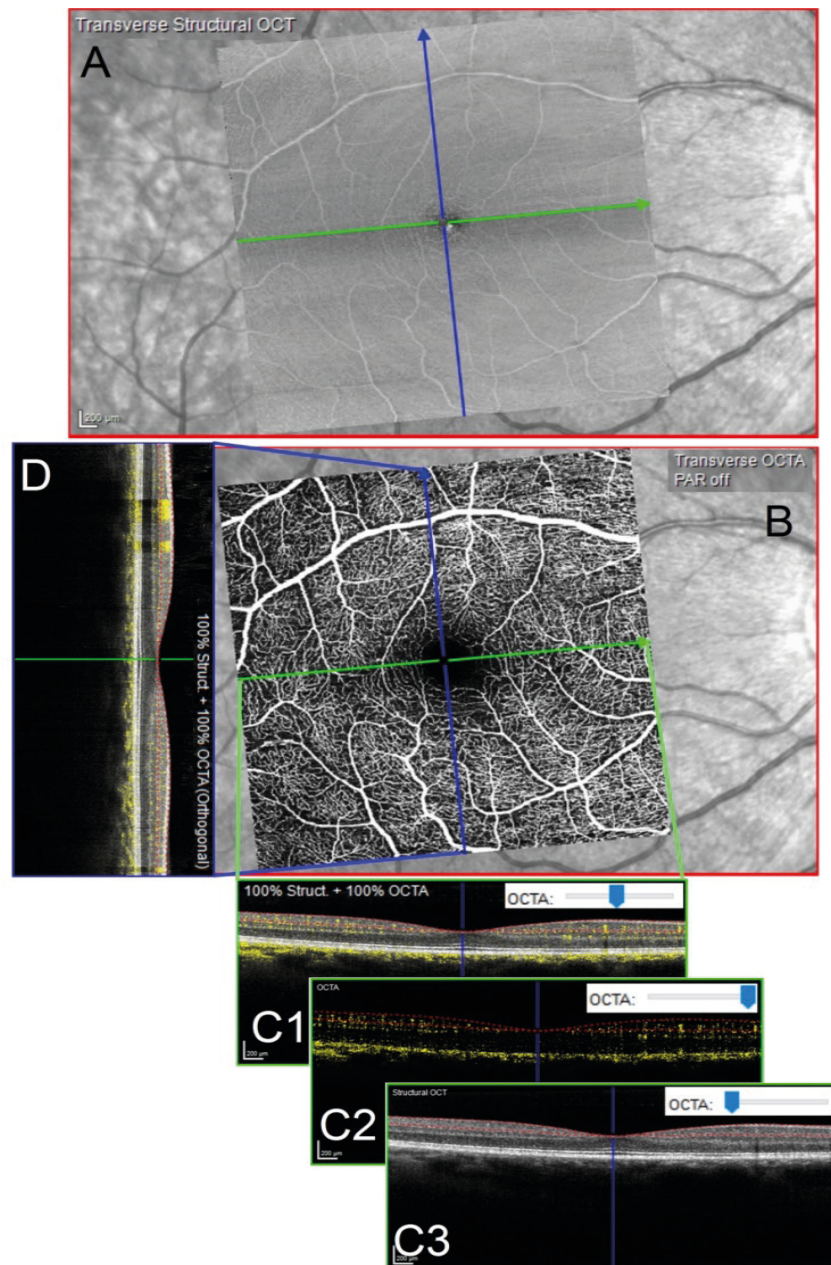

Figure 2: Review of OCT angiography data is mainly based on en face images and section images. A: En face image of the structural OCT data within the superficial vascular plexus. In the background, an infrared cSLO fundus image is shown. B: En face image of the corresponding OCTA data. C1-C3: OCT/OCTA fusion images of a section along the fast scanning axis (B-scan direction, green). C1: Section image shows structural OCT in the background and the OCTA data as yellow overlay. C2: Same as C1, but the structural OCT data is faded out via a slider. C3: Same as C1, but the OCTA data is faded out via a slider. D: OCT/OCTA fusion image where section is along the slow scanning axis (orthogonal to B-scan direction, blue).

Image Representation

The acquisition of OCTA volume scans provides a three-dimensional cube of data that includes structural OCT and OCTA images. A series of OCT section images (or B-scans) are acquired in order to create this cube of data.

En face images generated from slabs
Initial review of this data is usually based on images that are generated from slabs of the cube. Slabs are sections of 3D volumetric data. In the case of OCTA slabs, the section is delimited by anterior and posterior retinal and choroidal boundaries. The OCTA signal between these boundaries is displayed as a two-dimensional *en face* image, showing perfused vasculature; see **Figure 2 B**. It is referred to as "*en face* image" due to the transversal slab orientation; the resulting image gives the impression of looking onto the retina.

Section images

In the user interface, two kinds of section images are provided. One section image has the same orientation as the original B-scans (**Figure 2 C**) and the other section image corresponds to a section orthogonal to the original B-scans (**Figure 2 D**). To provide a direct visual correlation of structural and flow information, structural OCT section images and the corresponding blood flow information are combined into a fusion image; see **Figure 2 C1-C3** and **D**. This fusion image superimposes the OCTA signal on the structural OCT section image and shows the relation of the respective information. The relative transparency of the superimposed blood flow information and the structural information can be adjusted via a slider in the user interface.

The OCTA and OCT section images offer a detailed and precise correlation between retinal microstructures and perfused vessels. The *en face* images are optimal for visualization of retinal regions and the associated vascular networks (or plexuses) within specific retinal layers, as defined by slabs. The choice of these delimiting boundaries determines the tissue and associated vasculature that is represented in two-dimensional *en face* images.

Slab Definitions

The retinal vascular network can be divided in several vascular plexuses. In order to accurately detect and manage retinal vascular conditions, it is important to precisely discern the different retinal vascular plexuses. It is also important that slabs enable a continuous representation of the retinal and choroidal vasculature so that possible vascular abnormalities are not missed during image review. Currently, the differences in slab definitions often complicate the comparison of *en face* images between different devices.

The SPECTRALIS OCTA pre-defined slabs and their location within the retina and choroid are shown in **Figure 3**. The slab definitions of two other devices, and those proposed by Campbell et al. (2017)[9] are also shown to allow for a direct comparison.

To best separate the two distinct capillary plexuses within the deep vascular com-plex, Campbell et al. (2017) showed that slab boundaries can be defined based on the minima of the flow density profiles.[9] The SPECTRALIS OCTA slab definitions follow this concept for the intermediate capillary plexus (ICP) and the deep capillary plexus (DCP).[10] In order to reduce the number of anatomic interfaces required to calculate the boundaries, the intermediate capillary plexus (ICP) on the SPECTRALIS OCTA is derived based on constant offsets to the lower boundary of the inner plexiform layer (IPL). **Figure 4** (**C** and **D**) illustrates the precision that the SPECTRALIS OCTA slab definition offers in order to differentiate the distinct geometric vascular patterns present in the ICP and DCP. SPECTRALIS OCTA also separates the nerve fiber layer vascular plexus (NFLVP) from the superficial vascular plexus (SVP). In combination with the slab definitions of the avascular complex (AC), the choriocapillaris slab, and the choroid slab, a continuous representation of the retina is achieved. This definition of slabs (**Figure 3**) prevents from gaps being present as seen in other devices.
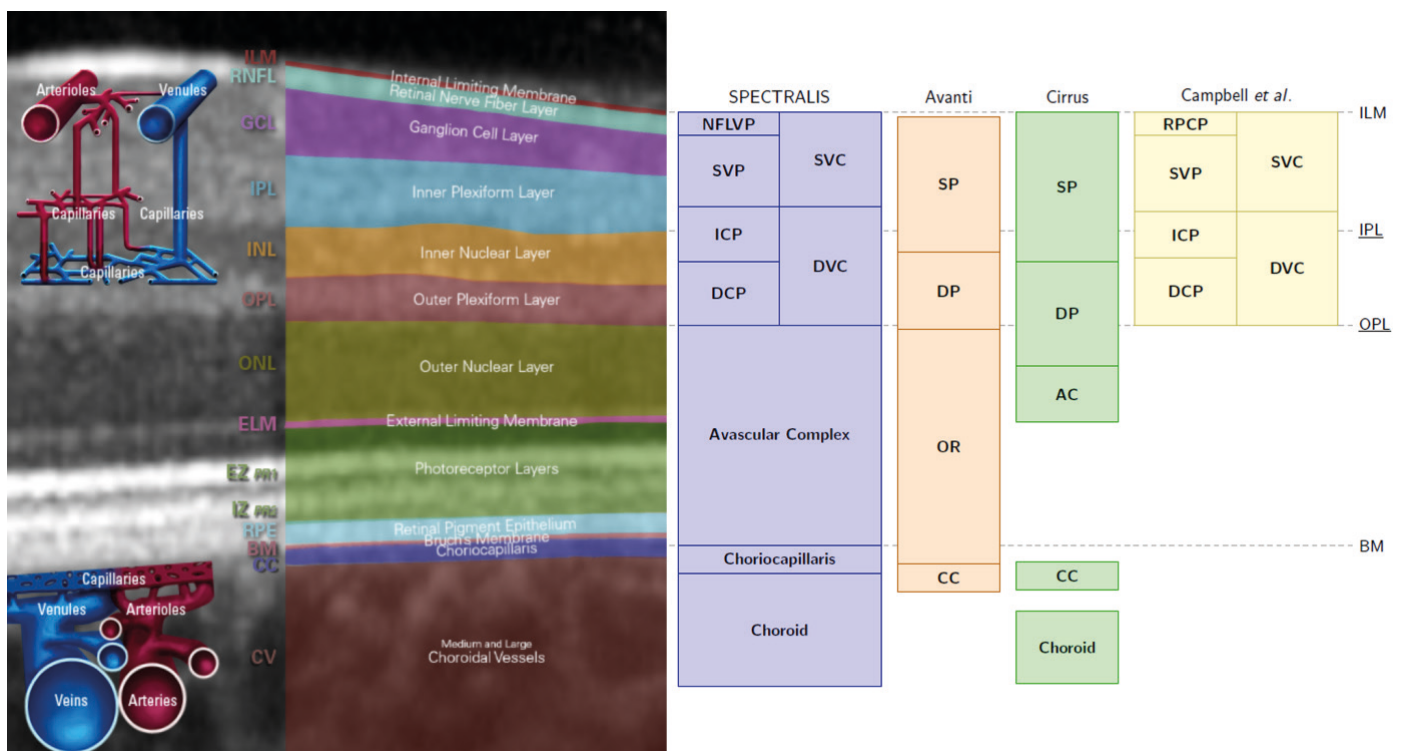

Figure 3: Definition of the slab boundaries. Left: Schematic figure of the layers and vessel networks in the human retina (Download here: www.he-academy.com/Retinal-Layers-Interactive). Right: Schematic figure of the slab definitions of SPECTRALIS, Avanti, Cirrus, and Campbell et al.[9] Abbreviations: SVC: Superficial Vascular Complex; NFLVP: Nerve Fiber Layer Vascular Plexus (part of SVC); SVP: Superficial Vascular Plexus (part of SVC); DVC: Deep Vascular Complex; AC: Avascular Complex; ICP: Intermediate Capillary Plexus (part of DVC); DCP: Deep Capillary Plexus (part of DVC); CC: Choriocapillaris /Choroid Cap; RPCP: Radial Peripapillary Capillary Plexus; SP: Superficial Plexus; DP: Deep Plexus; OR: Outer Retina.
Sources: SPECTRALIS: Heidelberg Engineering. OCT Angiography Module User Manual, Software Version 6.9, 2017. Avanti: Avanti Optovue. Optovue RTVue XR OCT Avanti System User Manual, Software Version 2016.1.0.26, 2016. Cirrus: Carl Zeiss Meditec Inc. CIRRUS HD-OCT User Manual Models 500, 5000, 2016. Campbell et al.[9]
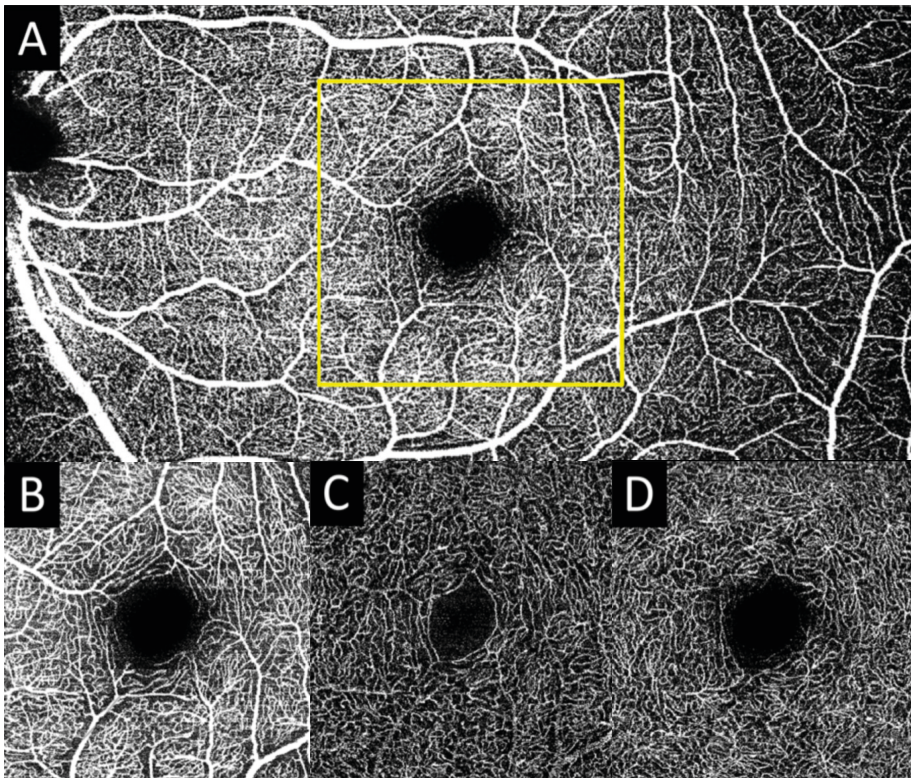
Figure 4: Comparison of two examinations of the same eye. A: En face image of the superficial vascular plexus (SVP) from 30°x15° scan acquired in High Speed mode (11 µm/pixel) providing a large field of view. B, C, and D: En face images acquired of a 10°x10° scan in High Resolution mode (5.7 µm/pixel). B: The small capillaries are better resolved in the SVP en face image of High Resolution scan, compare yellow outline in A which shows the same region of the same eye. C: The intermediate capillary plexus (ICP) can be clearly distinguished from the deep capillary plexus (D) due to the high axial resolution (~3.9 µm/pixel) of SPECTRALIS OCTA. The ICP and DCP vessel networks show clearly distinct geometric structures. In the DCP, star-like vascular intersections can be discerned, which likely represent connection to the venous superficial network.

Scan Patterns

SPECTRALIS OCTA offers flexible and selectable scan patterns with variable scan densities and fields, depending on the pathology of interest. For example:

A 30° x 15° (~8.8 mm x 4.4 mm) scan pattern provides a relatively large overview of the retinal and choroidal circulation; see **Figure 4 A**, ideal for detection of large vascular abnormalities or those that may not present at the central macula. This **high-speed** scan has a lateral resolution of 11 µm/pixel (comparable or even better than the resolution of other devices) and is useful for the evaluation of capillary dropout in retinal conditions such as diabetic retinopathy or retinal vascular occlusions.

A 10° x 10° (~ 2.9 x 2.9 mm) scan pattern with an isotropic lateral resolution of 5.7 µm/pixel (512 A-scans x 512 B-scans) offers the resolution needed to visualize the smallest capillaries; see **Figure 4 B**, **C** and **D**. Considering the small diameter of these smallest capillaries (approximately 8 µm)[11], a lower resolution scan may limit

the confidence in image interpretation as illustrated in **Figure 4** (**A** versus **B**).
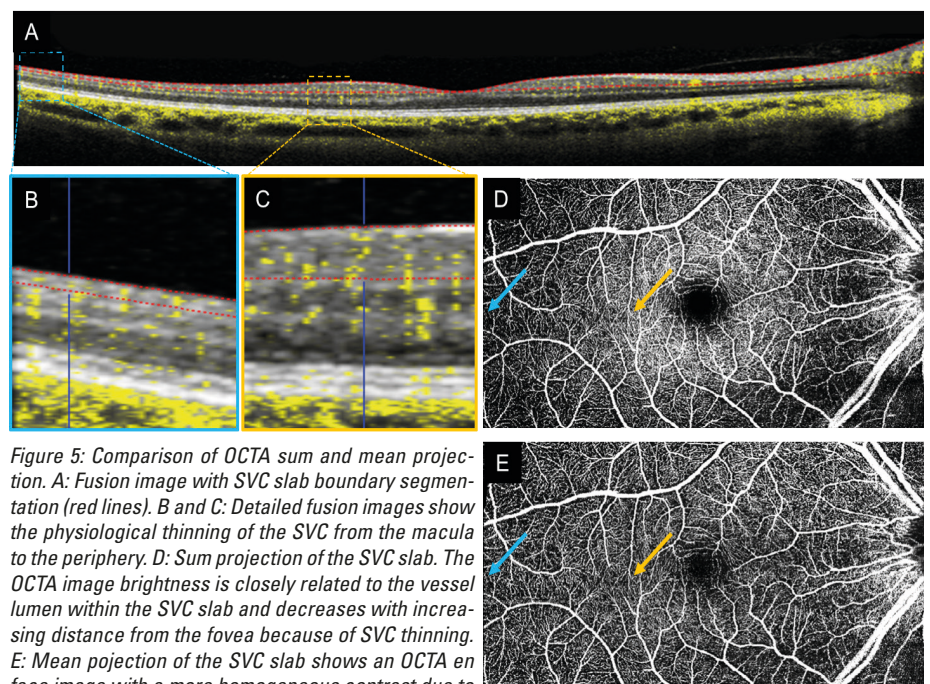
This **high-resolution** scan (5.7 µm/pixel)

Figure 5: Comparison of OCTA sum and mean projection. A: Fusion image with SVC slab boundary segmentation (red lines). B and C: Detailed fusion images show the physiological thinning of the SVC from the macula to the periphery. D: Sum projection of the SVC slab. The OCTA image brightness is closely related to the vessel lumen within the SVC slab and decreases with increasing distance from the fovea because of SVC thinning. E: Mean pojection of the SVC slab shows an OCTA en face image with a more homogeneous contrast due to normalization of the signal to the local slab thickness.

facilitates a more detailed and confident evaluation of vascular abnormalities at the capillary level.

Signal Intensity and Contrast Information

SPECTRALIS OCTA *en face* images are based on the sum of the OCTA signal between defined slab boundaries and a contrast function explained below.

As shown in the algorithm description, the SPECTRALIS OCTA signal is between zero for static tissue and one for each pixel within a perfused vessel. As a result, the sum projection provides an approximation of the total lumen of perfused vessels within a given slab.

The mean projection method, which is measured as the sum projection divided by the local slab thickness, leads to a direct correlation of the visibility of small capillaries with laterally varying slab thicknesses; see **Figure 5**. For OCTA image interpretation and analytics it is also important to consider the local thickness as the mean projection may result in an inhomogeneous representation of the capillaries in the *en face* images.

The resultant sum projection of SPECTRALIS OCTA images are converted to the final OCTA *en face* image by a contrast function designed to enable users to highlight different content within a given slab; see **Figure 6**. The sum of the
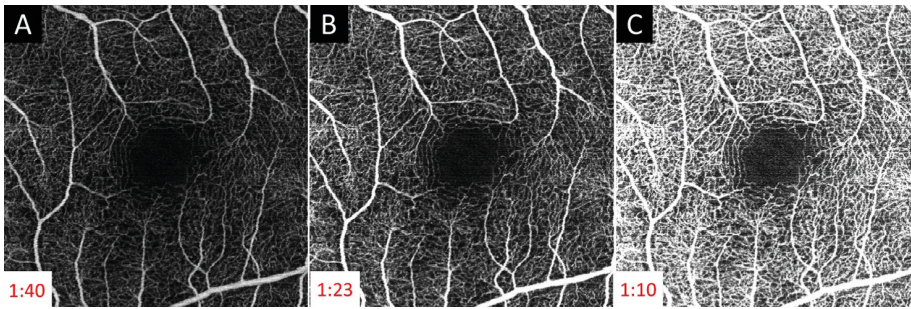
Figure 6: OCTA en face images (sum projection) of the full retina slab (from ILM to BM) with different contrast settings. A: the contrast is set to 1:40, producing a low contrast OCTA image that resembles an FA image. B: the contrast is set to 1:23, producing an OCTA image with more contrast that highlights smaller capillaries. With this setting, the brightness of larger vessels begins to saturate. C: the contrast is set to 1:10, producing an OCTA image with even more contrast where the en face image is becoming saturated since the full retina slab includes both the superficial vascular complex and the deep capillary complex.
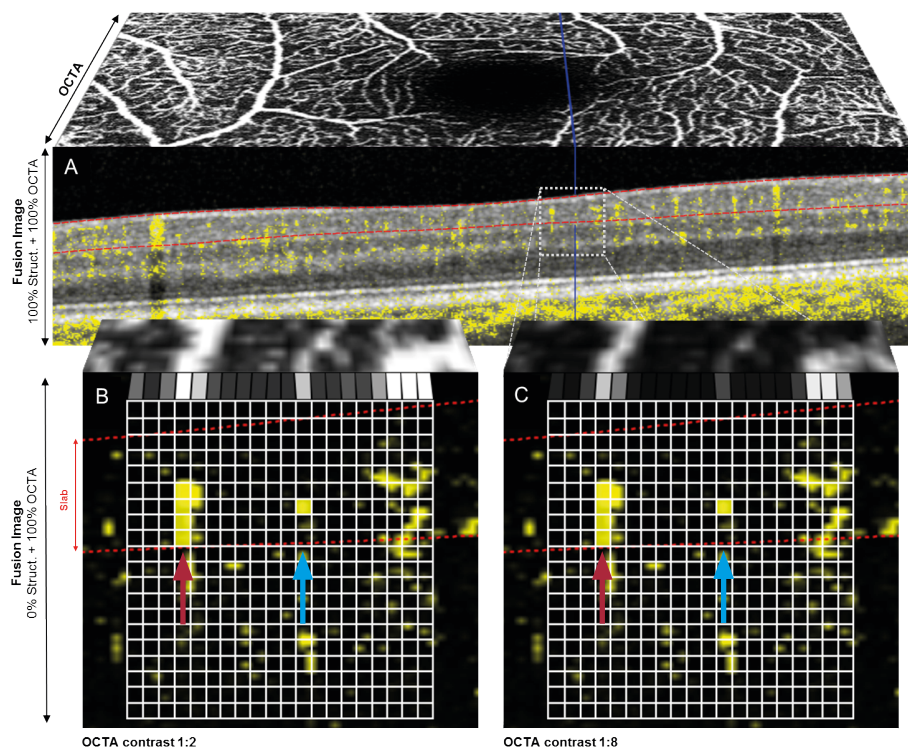

Figure 7: Illustration of sum projection and contrast setting for OCTA en face image calculation. The column sum of the OCTA values within the slab boundaries is computed. The red arrow highlights a larger superficial vessel where a sum value s=4 is obtained. The blue arrow highlights a small capillary where a sum value s=1 is obtained. The contrast setting determines, which sum value is mapped to white in the en face image. With a contrast setting of 1:c=1:2, the small capillary is visible (50% white), and the larger vessel appears saturated (100% white). When using a contrast setting of 1:c=1:8, the small capillary is barely visible (s/c means 12.5% white), and the larger vessel is no longer overexposed (s/c means 50% white).

OCTA signal in a given slab is converted into a gray value by a linear function. A sum projection value of 0 is always mapped to black. The sum projection value is mapped to white if it is greater or equal to a given value c; see **Figure 7**. The user has the ability to change the value of c with a slider control or to use an automatic setting. Reducing c will increase the contrast, therefore the user interface shows "1:c" to indicate the contrast setting. With higher contrast, the visualization of smaller structures such as small capillaries is improved. The lower the contrast, the better the visualization of thicker vascular structures (e.g. superficial arteries or larger choroidal neovascularizations) and the OCTA *en face* images better resemble FA images.

CURRENT LIMITATIONS AND SOLUTIONS

Adaptive Slab Feature

In some pathological eyes, the retinal layers are extensively disrupted and the default slab definitions are confounded. To provide a robust visualization of vasculature independent of the disruption of retinal layers caused by pathologies, SPECTRALIS OCTA provides an **adaptive retinal slab** which allows for a continuous and interactive display of the structures between the ILM and BM. The thickness of the adaptive retinal slab and its location within the retina can be changed interactively while the upper and lower slab boundaries automatically adapt to the shape of the ILM and BM, depending on which boundary the slab is closer to; see **Figure 8**.

Saved View

The SPECTRALIS OCTA also offers a function that allows the user to save a particular view (such as a view provided by the adaptive retinal slab or the view of a concrete lesion e.g. neovascular lesion). This view can later be recalled for a specific subject. This "**saved view**" function facilitates the ability to quickly recall and review a certain clinically relevant region within the retina or choroid of a specific eye, facilitating the comparison of images over time (follow-up).

Segmentation Correction

Considering that slabs are mainly defined by automatically segmented retinal layer boundaries, careful review of the segmentation is critical for correct interpretation of the *en face* projections. Segmentation failures especially occur in diseases where retinal layers are altered. For instance, intraretinal fluid, large pigment epithelial detachments, choroidal neovascularization, and certain atrophies often cause segmentation errors in most, if not all, state-of-the-art OCTA devices. Higher number of scans within an OCTA volume make the manual correction of such errors for each section image cumbersome. To facilitate the correction of an OCTA volume, SPECTRALIS OCTA provides a segmentation propagation tool. With this tool, segmentation correction of only a few scans leads to correction of compromised slab boundaries for the entire volume.

Projection Artifact Removal

Projection artifacts are frequently seen as a replication of more superficial vessels in posterior layers. While projection artifacts presented as the most common confounder early on in the inception of OCTA technology[4,12], this limitation has
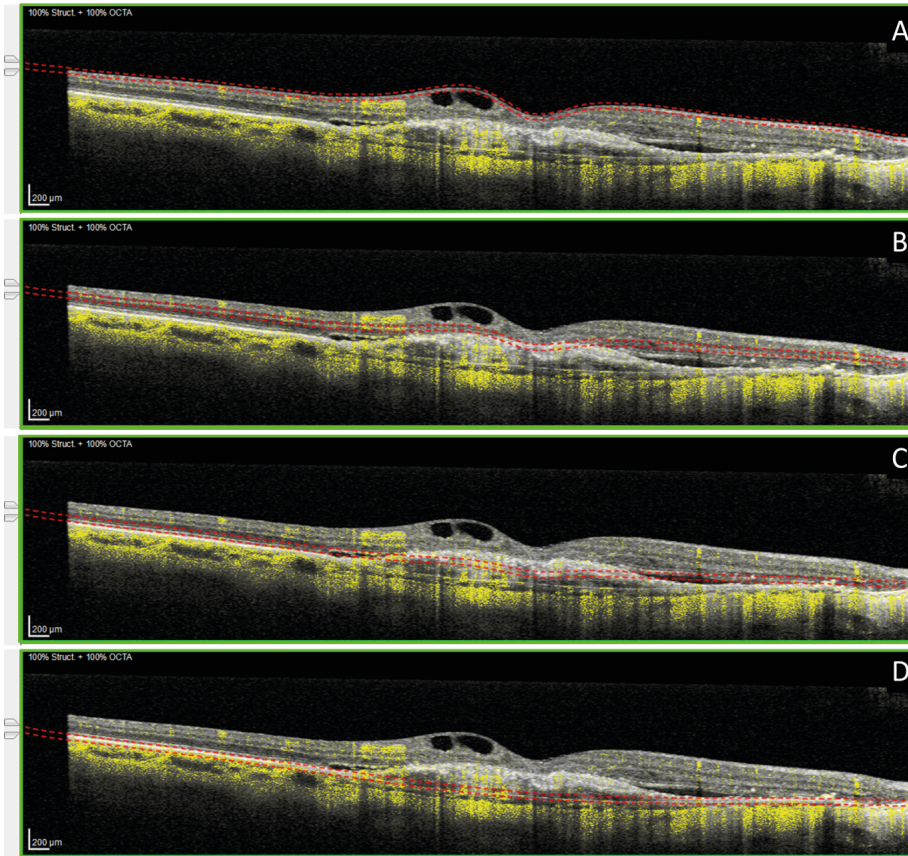
Figure 8: OCTA section images showing the Adaptive Slab feature. The shape of the slab is automatically adjusted to fit the ILM (A), demonstrated by dashed-red lines, and changes progressively (B, C) to adopt the shape of Bruch's membrane (D). The thickness of this slab can also be customized.

ers of high signal intensity, such as the retinal pigment epithelium. This is because for locations with high signal intensity, the distributions for static tissue and blood flow are expected to be very different and consequently even very small fluctuations are attributed to flow.

Projection artifact removal algorithms minimize these artifacts via post-processing. Some algorithms predominantly mask the regions below larger superficial vessels, which can introduce dark structures and seemingly disrupted vasculature in deeper layers[13,14]. This can lead to erroneous clinical interpretation. The SPECTRALIS OCTA projection artifact removal is geared to minimize the replication of superficial vasculature within deeper layers while leaving the vessel networks in deeper layers unaffected; see **Figure 9** (right). The user has the option to deactivate the projection artifact removal to review the integrity of the displayed data.

Multimodal Imaging

Before the advent of OCTA, diagnosis of ocular vascular pathologies was mainly based on dye-based fluorescein angiography (FA) and/or indocyanine green angiography (ICGA). These techniques provide two dimensional views of vasculature in the retina or the choroid. In contrast to OCTA, both methods provide a dynamic representation of vascular perfusion by depicting the in-flow of the injected dye via video images or a series of static images. In addition, dynamic information such as leakage of vessels and subsequent staining can be seen on dye angiography, but currently cannot be seen on OCTA images. However, FA and ICGA are invasive as they require dye-injection and therefore cannot be performed in every patient and/or during every patient visit. In contrast, OCTA is a non-invasive method that serves as a useful tool for frequent monitoring and even for screening of retinal vascular conditions. OCTA provides important three-dimensional structural and vascular information that FA and ICGA images are missing. In other words, FA/ICGA imaging and OCTA images provide somewhat complementary information and diagnostic value. The SPECTRALIS platform allows for integration of the OCTA modality with the gold-standard FA and ICGA modalities as well as with MultiColor and fundus autofluorescence fundus imaging, all using

been addressed in current state-of-the-art devices by means of post-processing; see **Figure 9**.

To understand the source of projection artifacts, it is important to know that the OCT beam has already passed through the more superficial layers before reaching and being reflected by deeper layers. The passage of light through larger superficial vessels leads to OCT signal fluctuation in deeper layers, even if nothing moves in the deeper layers. The signal fluctuates because the light has passed through and is altered by moving blood cells in a superficial vessel. Most (if not all) OCTA algorithms cannot distinguish these signal fluctuations from the fluctuations of moving particles within deeper layers[4]. For SPECTRALIS OCTA, the projection artifacts are more prominent in deeper lay-
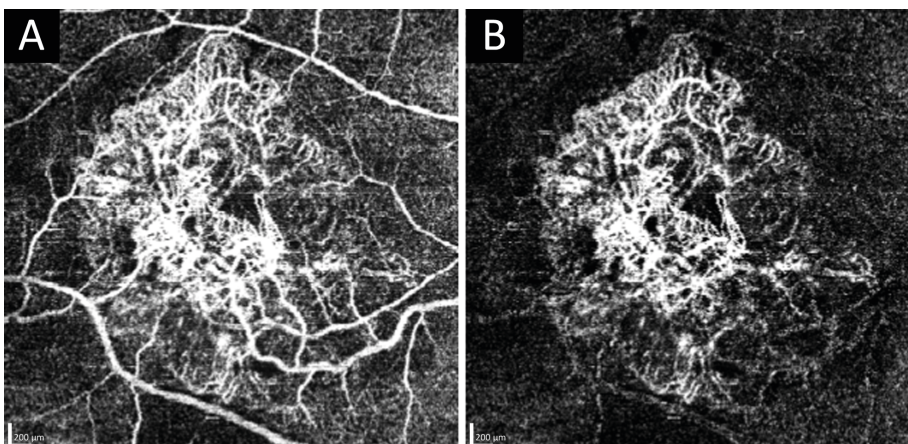

Figure 9: SPECTRALIS OCTA projection artifact removal. A subject with a large type 1 CNV was scanned in high-speed mode (11.4 µm/pixel). A: Without projection artifact removal, various large vessels seem to be connected with the neovascularization. B: After removal of the projection artifact, the actual size and the extent of the neovascularization can be appreciated.
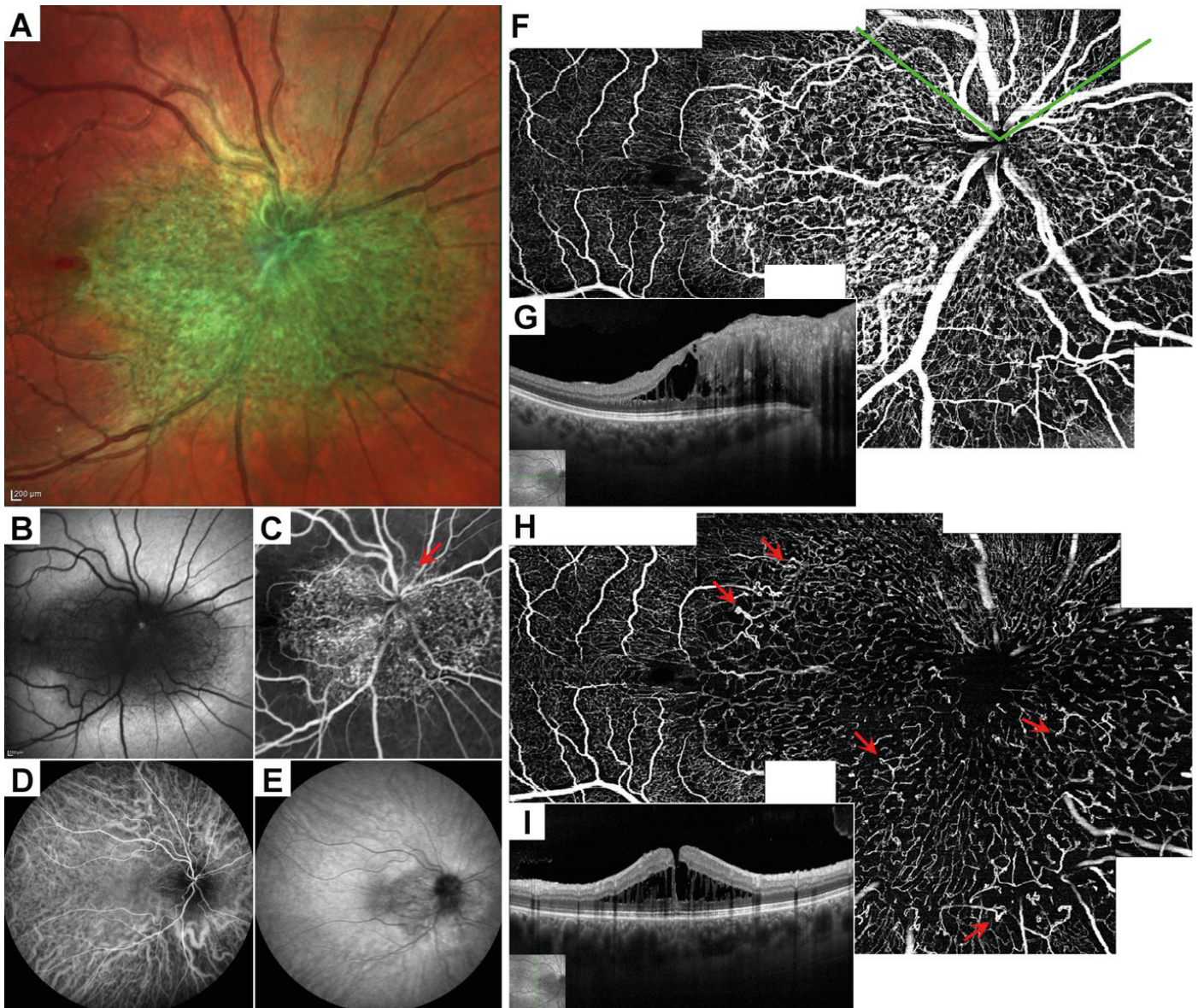
Figure 10: Multimodal imaging of a 35-year-old woman with combined hamartoma of the retina and retinal pigment epithelium. The MultiColor cSLO image (A) reveals a large juxtapapillary retinal fibrotic lesion. Fundus autofluorescence (B) exhibits the masking effect of this proliferation but confirms an otherwise intact RPE. Early-phase fluorescein angiography shows the vascular nature of the lesion as indicated by the arrow in C. Indocyanine green angiography indicates no choroidal involvement (D, E). The OCTA en face image, generated by a custom segmentation slab from the lower boundary of the ganglion cell layer to lower boundary of the inner nuclear layer, shows abnormal peripapillary vasculature in three quadrants caused primarily by structural changes associated with the lesion (F). The extent of the lesion is shown in the OCT structural scans (G-I). Another OCTA en face image (H), generated by a custom slab from retinal nerve fiber layer to ganglion cell layer shows similar structural changes but also reveals 'hairpin' loops, indicating the vascular origin of this lesion. Images provided courtesy of Dr. Marco Lupidi, Perugia, Italy.

confocal Scanning Laser Ophthalmoscopy (cSLO). The follow-up and the scan planning functionalities of SPECTRALIS further allow for the combination of these imaging modalities within one examination or over time. The diagnostic benefit of a multimodal imaging approach and the integration of OCTA can be illustrated with an example, as shown in **Figure 10**. Please refer to the figure caption for a detailed description. Altogether, the combination of these multimodal images led to a confident diagnosis of the tumor as a combined hamartoma of the retina and retinal pigment epithelium. OCTA elucida-

ted and confirmed the vascular origin of the lesion.

Scan Planning Tool

The SPECTRALIS Scan Planning Tool enables to set the desired location for an OCTA scan to be acquired, based on existing cSLO fundus and/or structural OCT images. To illustrate the clinical utility of the SPECTRALIS Scan Planning Tool, **Figure 11** shows an example of a patient with proliferative diabetic retinopathy. The patient was examined using FA imaging (**Figure 11 A**) and OCTA (**Figure 11 B**)

on the same day. The OCTA scan was centered on a region of interest using the SPECTRALIS Scan Planning Tool, based on the acquired FA images. This yields precise alignment of the imaging data and allows for a direct comparison of the different modalities. As can be seen, this proliferative diabetic retinopathy eye presented with a dense vessel network. The leakage of the dense network saturated the FA image, while OCTA images allowed for individual vessels to be discerned. Twelve days after treatment of the eye, a follow-up examination with OCTA was performed; see **Figure 11 C**.
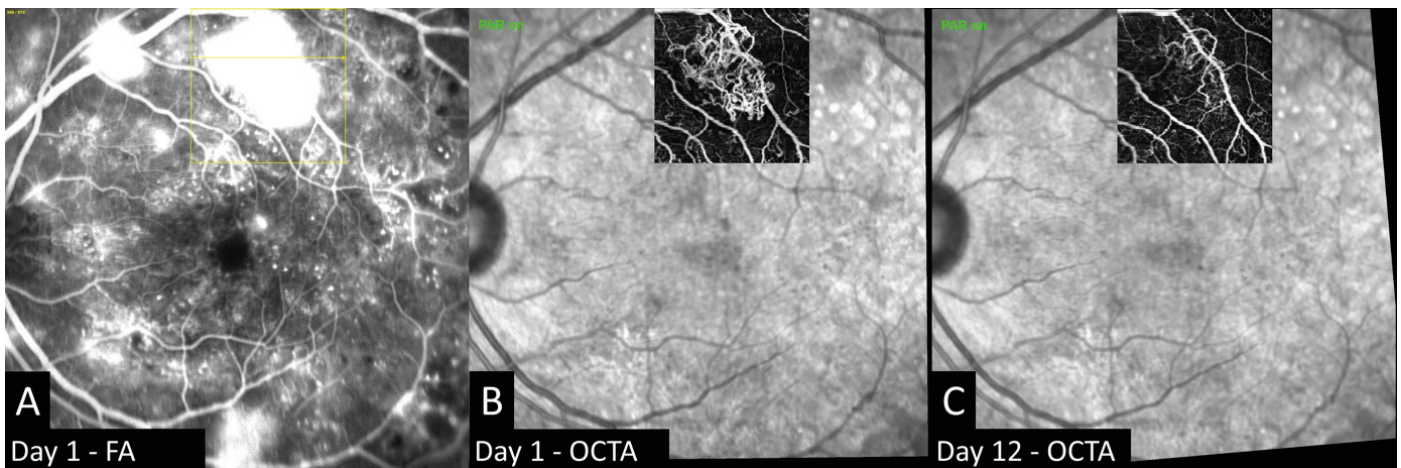
Figure 11: Multimodal integration of SPECTRALIS OCTA using the Scan Planning Tool and follow-up mode. A: The patient was imaged with fluorescein angiography on day 1, presenting with proliferative diabetic retinopathy. B: On the same day, an OCTA scan was acquired using the Scan Planning Tool in order to center the scan on the clinically relevant region. C: Twelve days later, treatment efficacy was controlled using the OCTA follow-up mechanism.

The follow-up scan was automatically acquired on the same location as on day 1, using the SPECTRALIS follow-up functionality, allowing for a direct comparison of the vessels and thereby a direct assessment of the treatment success. This case illustrates the clinical utility of the SPECTRALIS Scan Planning Tool, which effectively integrates both multimodal imaging and TruTrack™ follow-up imaging capabilities in order to facilitate confident diagnostic information. The combination of dye-based angiography and OCTA is coined "hybrid angiography". OCTA provides a non-invasive follow-up method to FA/ICGA and adds a third dimension to the precise localization of vascular flow.

FUTURE DEVELOPMENTS

Several functional extensions of SPEC-TRALIS OCTA are subject of active research and development. Currently, there are extensive developmental efforts geared towards reduced acquisition time, focus adjustment, and other usability improvements. There is also ongoing development towards expanding the field of view in order to allow for more streamlined assessment of vascular changes that are prevalent in the peripheral retina (e.g. diabetic retinopathy). Development of three-dimensional vessel segmentation is a key advancement that aims to improve the visualization of OCTA information (e.g. 3D rendering of vessels), and to enable reliable and enhanced analytics. In order to deliver robust OCTA analytics, the precision of the data is being thoroughly investigated and improved. There is ongoing research to establish the most appropriate methods of developing and visualizing normative data for capillary density measurements.[9,10] The relationship between vascular changes and retinal nerve fiber layer and ganglion cell layer thickness changes are being critically investigated with the intent to develop OCTA-based analytics optimized for glaucoma diagnostics. Moreover, OCTA analytics to show morphological changes (e.g. vessel tortuosity, vessel loops, interconnectivity, FAZ size, FAZ shape, microaneurysms) are being investigated, based on high-resolution SPECTRALIS OCTA images. High interest lies in robust methods to assess progression both analytically and visually, for management of glaucoma and the success of CNV treatment. Artificial intelligence (AI) methods are being explored as a means to facilitate early and automatic detection of vascular changes and prediction of disease progression. Recent research has highlighted the importance and relevance of axial and lateral resolution based on a prototype extension to SPECTRALIS OCTA.[15] The use of Dense B-scan OCTA (DB OCTA) software extension offers structural OCT and OCTA images with less speckle and noise, respectively.[15] This is a novel clinically useful tool that facilitates the correlation of retinal microstructures and blood flow more precisely than possible on current commercially available OCTA devices.[15] The DB OCTA feature is planned to be integrated into the SPECTRALIS software in order to help refine clinicians' understanding of a wide range of diseases and potentially improve clinical management of such disease.

CONCLUSION

In contrast to FA or ICGA images, OCTA provides 3D volumetric measurements of perfused retinal and choroidal vasculature. To help understand the differences between commercially available OCTA devices, this paper summarizes the principles and design considerations of SPECTRALIS OCTA.

The SPECTRALIS live eye tracking approach corrects for motion during acquisition, avoiding the need for extensive post-processing correction of geometric distortions. This precise and accurate tracking method may increase acquisition times, but is essential for accurate cross-sectional depiction of vasculature and the analysis of vascular changes over time, measured at consecutive visits. In order to avoid irreversible artifacts or loss in resolution that can be introduced by image enhancement filters (post-processing), it is important to save the data as raw as possible. The SPECTRALIS OCTA algorithm provides the raw probability of flow or no flow on a pixel basis (without loss in resolution). The SPECTRALIS OCTA is able to achieve high contrast between static tissue and flow and ensures that the *en face* image brightness is directly related to the lumen of perfused vessels within a slab. The defined vascular plexus slabs of the SPECTRALIS OCTA are designed to provide a continuous and

comprehensive visualization of the retina and choroid (leaving no gaps between the slabs), while effectively separating the different capillary networks. Novel software functions such as the fusion image (which enables the ability to study the spatial correlation of structure and flow) and the Dense B-scan OCTA (which provides higher quality scans) have been introduced to improve the clinical applicability of the technology.[15]

One potential confounding factor of OCTA imaging is projection artifacts. The root cause of such artifacts is described and the approach that the SPECTRALIS OCTA projection artifact removal employs to overcome such artifact is illustrated.

When vascular and/or retinal pathologies present, retinal layers are often extensively disrupted. These disruptions confound the OCTA default slab definitions. To mitigate this limitation, the SPECTRALIS OCTA provides an adaptive retinal slab feature which allows for a seamless and interactive display of the structures between the ILM and BM, by minimizing the dependency of the segmentation algorithm on the confounded inner and outer retinal boundaries. To facilitate the correction of segmentation boundaries in OCTA volume scans, SPECTRALIS OCTA provides a time-saving segmentation propagation tool. With this tool, segmentation correction of only a few scans leads to correction of compromised slab boundaries for the entire volume.

In addition to the high quality and resolution of the structural OCT *en face* images that accompany the SPECTRALIS OCTA data, the SPECTRALIS platform offers the ability to combine this data with other (gold standard) imaging modalities. The SPECTRALIS Scan Planning Tool allows for planning of OCTA scans, based on existing OCT, FA or ICGA images. This feature enables for a direct comprehensive assessment of retinal conditions while also facilitating the link between the different imaging modalities. This feature also offers the ability to acquire follow-up OCTA data based on previous examinations, which may include different imaging modalities. A comprehensive multimodal approach that includes OCTA improves the understanding of certain retinal pathologies and may enhance clinical decision making. SPECTRALIS OCTA offers many unique features that are clinically relevant, with future developments geared to further enhance its clinical applicability and hence further improve the confidence of its use in clinical decision making.

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