

Spektrum der Augenheilkunde

Volume rendering of superficial Optic Disc Drusen: a possible new Imaging technique using Optical Coherence Tomography Angiography --Manuscript Draft--

Manuscript Number:	SPEK-D-17-00013R1
Full Title:	Volume rendering of superficial Optic Disc Drusen: a possible new Imaging technique using Optical Coherence Tomography Angiography
Article Type:	S.I. : Medical Retina/Angio-CT
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Funding Information:	
Abstract:	<p>Background Optic disc drusen (ODD) are calcified deposits potentially caused by disturbances in axonal metabolism. The clinical course and visual impairment of ODD is usually mild, however, significant ocular morbidity may occur such as visual field defects and retinal haemorrhages. Optic disc drusen may pose a diagnostic dilemma and differentiating these from other entities that can lead to similar compressive axonal distress is imperative. We present a novel technique for three-dimensional (3D) characterisation of superficial ODD based on 3D volume rendering of optical coherence tomography angiography (3DOCTA) scans.</p> <p>Material and methods Optical coherence tomography (Zeiss Cirrus HD-OCT Model 5000 with AngioPlex) scans were obtained from the optic nerve head of a healthy 22 year old female. Consequently, 3D structural OCT data and OCTA were analysed enabling ODD segmentation and spatial characterization.</p> <p>Results Volumetric analysis of superficial ODD showed a maximal drusen horizontal diameter of 223 µm, maximal vertical diameter of 268 µm, surface area of 6'617 µm² and volume measurement of 12'875 µm³. The drusen were characterised by a connected network of multiple drusen islands instead of forming a dense mass. Multiple vascular channels with perforating vessels were found across the drusen.</p> <p>Conclusions</p>

	Three-dimensional volume rendering of OCTA scans provided new insight on the spatio-anatomical features of superficial ODD. The new features herein described, namely multilobulated drusen islands and intradrusen channels, may directly contribute to the pathogenic events leading to transient non-embolic visual loss and small vessel occlusion secondary to ODD.
Response to Reviewers:	We are pleased to submit a revised manuscript addressing the points that have been raised. We believe the reviewer's recommendations have allowed us to improve the paper.


Volume rendering of superficial Optic Disc Drusen: a possible new Imaging technique using Optical Coherence Tomography Angiography
Volume Rendering von oberflächlichen Optic Disc Drusen: eine mögliche neue Bildverarbeitung mit Optical Coherence Tomography Angiographie

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Peter Maloca is a consultant of Zeiss. Catherine Egan and Adnan Tufail were supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology. The other authors have no conflicts of interest. The views expressed are those of the author(s) and not necessarily those of the NEI, NHS, the NIHR, the Department of Health or Zeiss.

1 **Volume rendering of superficial Optic Disc Drusen: a possible new Imaging technique using**
2 **Optical Coherence Tomography Angiography**Volume Rendering von oberflächlichen Optic
3 **Disc Drusen: eine mögliche neue Bildverarbeitung** mit Optical Coherence Tomography
4 **Angiographie** 
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7 **Abstract**

8

9 **Hintergrund**



10 Drusen des **Sehnerven** (Optic Disc Drusen) stellen sich als verkalkte Ablagerungen dar, die
11 möglicherweise durch Störungen im axonalen Stoffwechsel verursacht werden. Obwohl diese Drusen
12 meist einen milden klinischen Verlauf zeigen und Sehbehinderungen selten sind, können sie mit
13 Gesichtsfelddefekten und Netzhautblutungen assoziiert sein. Optic Disc Drusen können diagnostische
14 Schwierigkeiten verursachen im Vergleich mit anderen Pathologien, die mit kompressiven axonalen
15 Störungen verbunden sind, wie Tumoren des Sehnerven. Daher werden neue bildgebende
16 Modalitäten wie die dreidimensionale Volumendarstellung der Optical Coherence Tomography
17 Angiography (3DOCTA) für eine bessere Visualisierung und das Verständnis von Optic Disc Drusen
18 angewendet.

19 **Material und Methode**

20 Bei einer 22-jährigen gesunden Frau wurden oberflächliche Optic Disc Drusen mit Optical Coherence
21 Tomography Angiographie (OCTA, Zeiss Cirrus HD-OCT Modell 5000 mit AngioPlex) abgebildet.
22 Dreidimensionales Struktur- und OCTA wurden überlagert, die Drusen segmentiert und vermessen.

23 **Resultate**

24 Die oberflächlichen Optic Disc Drusen zeigten einen maximalen horizontalen Durchmesser von 223
25 Mikrometer, einen maximalen vertikalen Durchmesser von 268 Mikrometer, die Oberfläche betrug
26 6'617 μm^2 und die Volumenmessung zeigte 12'875 μm^3 . Die Drusen zeigten keine ganz dichte
27 Masse, sondern stellten sich als ein verbundenes Netzwerk von Druseninseln dar. Mehrere offene
28 Kanäle wurden innerhalb der Drusen gefunden, durch welche Gefäße eindringen konnten.

29 **Schlussfolgerung**

30 Die dreidimensionale Volumendarstellung der Optical Coherence Tomography Angiographie bei Optic
31 Disc Drusen zeigte neue morphologische Merkmale wie multilobulierte Druseninseln und Kanäle
32 innerhalb der Drusen, die für die Netzhautperfusion im Falle einer Gefäßokklusion kritisch sein
33 können.

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36 **Background**

1
2 37 Optic disc drusen (ODD) are calcified deposits potentially caused by disturbances in axonal
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4 38 metabolism. The clinical course and visual impairment of ODD is usually mild, however, significant
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6 39 ocular morbidity may occur such as visual field defects and retinal haemorrhages. Optic disc drusen
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8 40 may pose a diagnostic dilemma and differentiating these from other entities that can lead to similar
9
10 41 compressive axonal distress is imperative. We present a novel technique for three-dimensional (3D)
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12 42 characterisation of superficial ODD based on 3D volume rendering of optical coherence tomography
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14 43 angiography (3DOCTA) scans.

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16 44 **Material and methods**

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18 45 Optical coherence tomography (Zeiss Cirrus HD-OCT Model 5000 with AngioPlex) scans were
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20 46 obtained from the optic nerve head of a healthy 22 year old female. Consequently, 3D structural OCT
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22 47 data and OCTA were analysed enabling ODD segmentation and spatial characterization.

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24 48 **Results**

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26 49 Volumetric analysis of superficial ODD showed a maximal drusen horizontal diameter of 223 μm ,
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28 50 maximal vertical diameter of 268 μm , surface area of 6'617 μm^2 and volume measurement of 12'875
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30 51 μm^3 . The drusen were characterised by a connected network of multiple drusen islands instead of
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32 52 forming a dense mass. Multiple vascular channels with perforating vessels were found across the
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34 53 drusen.

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38 55 **Conclusions**

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40 56 Three-dimensional volume rendering of OCTA scans provided new insight on the spatio-anatomical
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42 57 features of superficial ODD. The new features herein described, namely multilobulated drusen islands
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44 58 and intradrusen channels, may directly contribute to the pathogenic events leading to transient non-
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46 59 embolic visual loss and small vessel occlusion secondary to ODD.

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50 61 **Schlüsselwörter**

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52 62 Three-dimensional volume rendering - Optical coherence tomography angiography – Optic disc
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54 63 drusen

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58 65 **Key words**

66 Three-dimensional volume rendering - Optical coherence tomography angiography – Optic disc

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69 **Introduction**

1
2 70 Optic disc drusen (ODD) are acellular deposits composed of mucoproteins, mucopolysaccharides and
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4 71 iron which undergo progressive calcification [1]. The size and number of ODD vary considerably and
5
6 72 they can be found at all prelaminar levels. Smaller ODD tend to be located more proximal to the
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8 73 lamina cribrosa [2]. The clinical course of ODD is usually benign, although they can be associated with
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10 74 visual field defects [3-6], retinal haemorrhages [7-9], optic nerve fiber compression and partial optic
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12 75 nerve atrophy, and juxtapapillary retinal scarring [2]. Diagnosis of ODD is usually based on
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14 76 funduscopy appearance, ultrasonography and fundus autofluorescence. Visual field testing or spectral
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16 77 domain optical coherence tomography (SDOCT) [10-13] may also be of utility. In SDOCT,
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18 78 ophthalmoscopically visible ODD appear as multiple lumps mostly inside the disc with highly reflective
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20 79 borders and internal spaces. Buried ODD appear as a C-shaped mass outside the disc with relatively
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22 80 less distinct borders [12].
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24 81 We present a novel technique characterised by 3D volume-rendering of OCTA scans (3DOCTA) of
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26 82 superficial ODD. This approach enhances the diagnostic abilities of non-invasive angiography whilst
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28 83 giving new insight on the spatio-anatomical features and how these integrate with angiographic
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30 84 findings of superficial ODD.
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85 **Methods**

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2 86 Our technique was applied to OCT scans obtained in a 22 year old Caucasian female. Informed
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4 87 consent was obtained from her for being included in the study. On ophthalmologic examination, best
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6 88 corrected visual acuity was 20/15 and 20/15 in the right and left eyes, respectively. There was no
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8 89 relative afferent pupillary defect. Intraocular pressure was within normal range and colour vision was
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10 90 normal (Ishihara test plates). The anterior chambers and vitreous were clear in both eyes. Fundus
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12 91 examination revealed bilateral superficial ODD with corresponding hyperautofluorescence on
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14 92 autofluorescence imaging.

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16 93 Autofluorescence and OCT imaging was performed using the Heidelberg Spectralis (Heidelberg
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18 94 Engineering, Heidelberg, Germany). The following OCT parameters were used: 15° scan angle, with a
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20 95 scan area 4.4 mm x 4.4 mm x 1.9 mm, Enhanced Depth Imaging on, 73 B-scans with an interslice
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22 96 distance of 61 µm. Imaging with OCT was averaged for 9 scans using the automatic averaging and
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24 97 tracking feature.

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26 98 The OCTA measurements (3 mm x 3 mm scan area, 245 x 245 pixel) were performed with the Zeiss
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28 99 Cirrus HD-OCT Model 5000 with AngioPlex (Review software 9.0.0.281, Carl Zeiss Meditec, Jena,
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30 100 Germany). All en-face OCTA cutting planes were exported into a 3D OCTA stack. In addition, all
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32 101 structural OCT en-face images were exported into a 3D structural OCT stack (3DOCT). Both image
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34 102 stacks comprised of structural OCT volume (3DOCT) and flow information volume (3DOCTA), were
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36 103 aligned and overlaid. The spaces occupied by ODD were manually segmented by thresholding of
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38 104 pixel intensity. A threshold from 0 to 70 grey-scale units (scale 0 to 255) enabled delineation and
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40 105 separation of the individual lesions. Image artifact from surrounding vessel shadowing was excluded.
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42 106 After segmentation, volume and surface measurements were performed. Finally, all compartments
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44 107 were integrated into one combined volume of structural OCT, OCTA and segmented drusen to study
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46 108 the topographic relationships between vessels and drusen in 3D.

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110 **Results**

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2 111 The clinical diagnosis of ODD was confirmed on autofluorescence imaging. Two large drusen were
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4 112 identified in the nasal superior quadrant of the left optic nerve head (ONH ; Fig. 1).

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6 113 Segmentation of the drusen revealed a maximal drusen horizontal diameter of 223 μm , maximal
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8 114 vertical diameter of 268 μm , surface area of 6617 μm^2 and volume measurement of 12'875 μm^3 . A

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10 115 close relationship of the ODD with the surrounding vessels was identified on 3DOCTA (Fig. 2) which in
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12 116 addition revealed the presence of several notches on the surface of the ODD ("drusen indentations").

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14 117 In the structural OCT, superficial drusen had a round appearance and appeared hyperreflective with a
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16 118 granular aspect.

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18 119 On the OCTA, the vessel signal density, though reduced, was not entirely devoid of signal. A fainter
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20 120 signal stemming from small vessels could be detected in the hyporeflective areas occupied by the

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22 121 ODD (Fig. 2B). The drusen appeared as islands encroaching these smaller vessels, forming
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24 122 interconnecting vascular channels ("drusen channels").

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125 **Discussion**

1 126 The use of 3DOCTA enabled the identification of new morphological features and interactions in ODD.

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4 127 This new technique facilitated the diagnosis, visualisation and volumetric characterisation of ODD. In
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6 128 contrast to other imaging methods, namely two-dimensional standard OCT [11, 14, 15] and
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8 129 autofluorescence imaging [13, 16], a much more detailed drusen microanatomy with the presence of
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10 130 multilobulated, interconnected drusen lobes was found on combined three dimensional structural OCT
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12 131 and 3DOCTA. Several drusen were organised into a "drusen cluster", whereas others were singular. A
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14 132 new metric approach was provided to measure not only the vertical and horizontal drusen diameter,
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16 133 but to define single drusen surface and volume as well. Potentially, this technique can guide to a
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18 134 specific "drusen cluster matrix". This could be helpful to document drusen's state of equilibrium or
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20 135 express characteristics for drusen dynamics, e.g. fusing of drusen into a cluster. Distinct parameters
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22 136 can be used to monitor the interconnections with other clusters and to classify the clusters and lobules
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24 137 which in turn could be used to document growth and assess mechanical properties. The ability to
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26 138 visualise and perform volumetric and surface measurements in ODD serves as a potential diagnostic
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28 139 and follow-up tool. It may also provide new insight on the pathogenic mechanisms of ODD-related
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30 140 ischaemic events such as retinal occlusion, choroidal neovascularisation [17-19], non-arteritic
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32 141 ischaemic optic neuropathy and peripapillary subretinal haemorrhages [7, 20-22].

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34 142 Our method revealed another interesting finding. ODD are not a compact circumscribed mass but
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36 143 show several openings ("drusen channels"), through which persisting vessels penetrate (Fig. 3).
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38 144 Calcification of ODD and aggregation formation may potentially contribute to obstruction of the
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40 145 capillary network with consecutive anatomical and functional damage of the retinal nerve fiber layer
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42 146 (RNFL) [23]. It may be a seemingly simple question of what governs and adjusts the geometry of
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44 147 these drusen channels. However, it may be a challenge to develop new morphodynamic models that
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46 148 should be addressed by future research. Implementation of this technique in clinical practice will
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48 149 depend on further temporal analysis of ODD.

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50 150 In this patient, the ODD showed a very close relationship to the ONH vessels. Arguably, depending on
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52 151 the nature and consistency of the ODD material, the elasticity of the surrounding vessels could be
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54 152 restricted or endovascular changes such as inflammatory effects originated on the drusen surface
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56 153 could be triggered [2] which could lead to a transient or permanent restriction of the vessel perfusion.

154 There are several limitations to our study. Only superficial drusen were examined and the number of
1 155 drusen was too low for us to extrapolate our findings to all superficial ODD. The segmentation of the
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4 156 drusen was performed manually with threshold filtering which may lead to artifacts depending on the
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6 157 levels of the threshold and the speckle noise signal. Furthermore, a general accepted threshold level
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8 158 is not defined yet. As OCTA is based on the motion contrast to show blood flow, the visualisation of
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10 159 the vessel signal may be limited because of artifacts due to OCT image acquisition, eye motion, or
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12 160 image processing [24].

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14 161 This study describes the first use of a new imaging technique, 3DOCTA, applied to superficial ODD.

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16 162 This technique enabled the characterisation of new morphological features of superficial ODD which,
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18 163 to the best of our knowledge, had never been reported. This technique may provide new insight on the
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20 164 pathogenic mechanisms associated with symptomatic ODD.

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167 All procedures followed were in accordance with the ethical standards of the responsible committee on
1 human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as
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3 revised in 2008 (5).
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226 **Figures**

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229 Fig. 1. Fundus imaging of optic disc drusen (ODD) in a 22 year old healthy female. (A) Scanning laser
1 ophthalmoscopy scan of the right optic nerve shows an elevated optic disc with no features of optic
2 230 disc edema. Multiple, pinpoint-like lesions are seen in the nasal superior quadrant. (B) Corresponding
3 231 autofluorescence scan of the right eye showing hyperautofluorescence and confirming the diagnosis
4 232 of ODD.
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237 Fig. 2. Image processing for three-dimensional OCT volume rendering of optical coherence
1 tomography angiography (3DOCTA). (A) En-face-view of optic disc drusen (ODD) (arrow) which
2 238 demonstrates a hyperreflective area between two hyporeflective vessels (arrow head). (B)
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4 239 Corresponding en-face optical coherence tomography angiography (OCTA) scan of the optic disc
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6 240 depicted in (A) at an identical level. In the area of superficial ODD, an ovaloid area of poor signal is
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8 241 seen (arrow). Minor signals are detected inside the ovoid space. The two hyporeflective vessels
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10 242 around the drusen appear to be pushed outwards. Larger optic disc vessels are separated from
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12 243 smaller vessels by their caliber (arrow heads). (C) 3DOCTA of the same eye shows an elevated
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14 244 vascular network which is a typical feature of ODD. (D) En-face 3D volume rendering shows a signal
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16 245 void area of drusen with visualisation of the white image background. Clearly, the adjacent large
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18 246 vessels (arrow head) are dislocated by the drusen. (E) Drusen are not depicted in the 3D volume
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20 247 rendering of structural OCT. The white spot reflects condensation of posterior vitreous. (F) Combined
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22 248 volume rendering of structural and OCTA of the same optic disc.
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253 Fig. 3. Combined volume rendering optical coherence tomography (OCTA) and segmented optic disc
1 drusen (ODD). (A) Two drusen are visible on the surface of optic disc OCTA (arrows). Smaller,
2 254 drusen (ODD). (A) Two drusen are visible on the surface of optic disc OCTA (arrows). Smaller,
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4 255 persisting vessels are seen within the ODD, corresponding to the granular OCTA signals in Fig. 2B.
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6 256 Larger vessels wind around the ODD (arrow head). (B) Same volumetric analysis as in (A) in a more
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8 257 posterior cutting plane demonstrates that the ODD are not a uniform corpuscle, but are composed of
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10 258 at least four islands of interconnected extravascular material. (C) After segmentation, the ODD are
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12 259 shown to consist of several smaller lobules partly connected by fine bridges, contrary to their
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14 260 appearance on autofluorescence as a dense compact mass (Fig. 1B). (D) Magnification of the upper
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16 261 left ODD in (C). 3D volume rendering enabled the identification of small openings from within the ODD
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18 262 through which persisting vessels emerge ("drusen channels", arrow head). The surface of the ODD is
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20 263 irregular and several notches are visible ("drusen indentations", arrows).

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