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APOSTEL-R Recommendations for Reporting Retinal Optical Coherence Tomography Studies in Rodents

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Abstract

Background and Objectives

Retinal optical coherence tomography (OCT) in rodent models has been used to longitudinally image retinal changes, to define end points for more costly or time-consuming experiments, and to better understand the pathophysiology underlying OCT findings in human diseases. No standardization of rodent OCT reporting currently exists. Here, we aim to establish consensus recommendation for reporting results from retinal OCT studies in rodents.

Methods

Initial recommendations were developed based on the APOSTEL criteria for quantitative OCT reporting in humans by a core team. Using a modified Delphi process, an expert panel of rodent OCT researchers (N = 31) and the wider scientific community discussed, refined, and voted on these initial recommendations. The list of recommendations was then revised and approved by the expert panel.

Results

The final 7-point checklist includes reporting recommendations regarding the study protocol, OCT device, acquisition settings and modifications, scanning protocol, funduscopic imaging, postacquisition data selection and image data analyses, and qualitative and quantitative results. With a median agreement score of 3 or 4 out of 4, the scientific community agreed with these recommendations. After revisions, the expert panel accepted the final recommendations.

Discussion

The Advised Protocol for OCT Study Terminology and Elements for reporting OCT studies in rodents (APOSTEL-R) originates from an expert consensus. They will provide guidance throughout the experimental process and will contribute to the standardization and quality improvement of preclinical OCT studies.

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Supplementary Material

Introduction

Optical coherence tomography (OCT) uses the interference of near-infrared light to produce high-resolution cross-sectional images of tissue. Retinal OCT has been used for decades in ophthalmology, neurology, and neuroophthalmology to diagnose ocular diseases and to quantify axonal and neuronal loss caused by retinal diseases, optic neuropathies, and CNS diseases (e.g., neurodegenerative, inflammatory, vascular).

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Glossary

IQR = interquartile range; **OCT** = optical coherence tomography.

Retinal OCT in rodent models has been used (1) to better understand OCT findings in human diseases in a back-translational approach, (2) to longitudinally image structural retinal changes in near-to-cellular resolution to reduce the number of animals and to avoid pseudo-longitudinal histologic analyses, and (3) to define optimal end points for more costly or time-consuming experiments such as single-cell RNA sequencing.[1-5] Although OCT imaging acquisition, quality control, and reporting have been standardized by the international multiple sclerosis visual system consortium (IMSVISUAL) and others for use in human subjects, this is not the case for retinal OCT imaging in rodents.[6-11] With more than 1,000 articles in PubMed to date, there is a plethora of data collection and reporting approaches that do not exploit the full potential of the method with respect to reproducibility, interstudy comparability, and generalizability of findings and may even lead to missing pieces of information. Even when focusing on outstanding recent examples of preclinical and translational work in ophthalmology and neurology where the methods are described with great care, the apparent lack in standardization may reduce interstudy comparability.[12-21] Common gaps in rodent OCT reporting include (1) incomplete reporting of imaging parameters (e.g., field of view, A/B-scan number, averaging protocols, number of repeated scans, wavelength, and resolution for custom devices), (2) incomplete description of animal and experimental context (e.g., species, strain, age, anesthesia protocol and hydration/temperature control), (3) limited quantitative reporting (e.g., quality control, segmentation criteria, and baseline/normative data), (4) insufficient data visualization (e.g., scale bars, labels, and scan location), (5) inadequate statistical reporting (e.g., sample size justifications, blinding/randomization), and (6) missing reporting of technical modifications (e.g., positions, pupil dilatation, and calibration).

We, here, report the Advised Protocol for OCT Study Terminology and Elements recommendation in rodents (APOSTEL-R recommendations) obtained with a modified Delphi process. These recommendations are meant to guide researchers in their choice of selecting and structuring core methodical characteristics and results for their data presentation in lectures and manuscripts. Adhering to these recommendations will help to advance research and possibly also to reduce the number of experimental animals in preclinical OCT imaging studies.

Methods

The APOSTEL-R recommendations were developed using a modified Delphi method—a systematic framework that makes use of multiple rounds of questionnaires to achieve expert consensus on a specific question (Figure). First, the APOSTEL 2.0 recommendations (for application in humans) were critically reviewed and revised for an application in rodents by a core team (F.C.O., M.D., W.L., P.A.) based on recent scientific literature. An expert panel (N = 31; see author list) was then asked to evaluate the drafted recommendations and provide feedback through email. The members of the panel are experts for or corresponding authors of OCT studies in rodents or were referred by corresponding authors of OCT studies.

Experts in the field, evidenced by at least 5 high-impact publications on rodent and human OCT studies with strong translational relevance, were selected as members of the expert panel. Subsequently, the wider scientific community was invited by consortia email lists (international multiple sclerosis visual system consortium (IMSVISUAL) and regional/national lists) to provide feedback using a free online survey via Google Forms (eAppendix, Google Forms): All participants self-selected within 1 month from the first invitation and then had to rate their agreement for each item of the recommendations on a scale from 1 (full disagreement) to 4 (full approval) and were able to add optional comments if desired. The scores are reported as median, interquartile range (IQR). The aggregated results of this online survey were then reviewed by the expert panel. Finally, the members of the expert panel were then asked to approve or reject the final list of recommendations in an anonymous majority vote using an additional online questionnaire.

Results

Consensus Process

Based on the APOSTEL 2.0 recommendations, the core team first suggested 31 recommendations in 7 categories: (1) study protocol, (2) OCT device, (3) acquisition settings and modifications, (4) scanning protocol, (5) fundoscopic imaging, (6) postacquisition data selection and image data analyses, and (7) qualitative and quantitative results. Based on the feedback of the expert panel, 2 recommendations were added to category 7, and 16 recommendations across categories were revised.

Forty-one scientists participated in the online survey; 13 scientists had less than 1 year of experience with OCT in rodents, whereas 21 scientists had more than 5 years of experience. All scientists with less than 1 year of experience with OCT in rodents are established experts in clinical OCT research and were invited to gain their valuable methodical input. All 33 recommendations developed by the expert panel

Figure Modified Delphi Method Used to Establish the APOSTEL-R Criteria

(1) The APOSTEL-R recommendations are based on the APOSTEL 2.0 recommendations for humans, which (2) were first adapted for application in rodents by a core team. Then (3) feedback by a panel of 31 experts was collected and the criteria were revised. (4) Using an online survey, feedback by the scientific community (N = 41) was collected. (5) The revised criteria were approved by the expert panel.

were approved with a median score of 3 or 4. In category 1 [study protocol], 2 [OCT device], and 4 [scanning protocol] all recommendations received a score [median (IQR)] of 4 (4, 4) indicating full agreement. Within the group of experts with >1 year experience, the recommendations also received a median score of 4.

In category 3 [acquisition settings and modifications], the recommendation 3.1, "Report on the holder used and/or the bedding/supportive devices (e.g., heat pad) of the rodent during examination," received a score of 3 (3, 4). All other recommendations in this category including on 3.2 anesthesia, 3.3 pupil dilatation, 3.4 eye drops, 3.5 contact lenses, 3.6 device modification, and 3.7 perpendicular alignment also received a score of 3 (3, 4). Within the group of experts with >1 year experience, scores for all recommendations remained stable or improved (for pupil dilatation and device modifications: 4 (4, 4)). All comments were either focused on the importance of detailed recommendations or questioning the relevance of such detailed reporting.

All recommendations in category 5 [funduscopic imaging] including on 5.1 potential other imaging modalities, 5.2 acquisition protocols for all used imaging modalities, and 5.3 device-specific features if used received a score of 4 (3, 4). Within the group of experts with >1 year experience, recommendation also received a median score of 4. Comments included for example suggestions (1) to report the order of acquisition, (2) to add methodical details to the supplement, and (3) to only include the methods, for which data are reported.

In category 6 [postacquisition data selection and image data analyses], the recommendations on 6.1 quality assessment, 6.3 eye selection for analysis, 6.4 analysis software, 6.5 included retinal layers, 6.6 segmentation method, and 6.7 grid type received full approval with a score of 4 (4, 4) by the panel as well as by experts with >1 year experience. The recommendations on 6.2 postacquisition exclusions and 6.8 pixel to millimeter ratio received a score of 4 (3, 4) by the panel. Within the group of experts with >1 year experience, the score for recommendation 6.8 remained stable and for recommendation 6.2 improved to 4 (3.75, 4). Comments included suggestions (1) to standardize quality control of rodent OCT imaging and (2) to specifically report if artificial intelligence–based methods were used for segmenting—as well as outlining the importance of this section.

In category 7 [qualitative and quantitative results], the recommendations on 7.1 anatomic structure, 7.2 measurement units, 7.3 eyes with abnormalities, and 7.4 statistical modeling received full approval with a score of 4 (4, 4) by the whole panel as well as by experts with >1 year experience. Recommendations on displaying 7.5 individual data and 7.6 absolute and relative longitudinal data received a score of 4 (3, 4) by the whole panel as well as by experts with >1 year experience. Comments included a suggestion to make an illustrative or segmented OCT image mandatory and outlining the importance of reporting the number of analyzed eyes and mice.

The revised criteria were accepted by 100% of the expert panel (22/22 votes). The different versions of the APOSTEL-R recommendations and anonymized survey results are available from the corresponding author at reasonable request.

Summary of Recommendations

The results of the consensus process were evaluated and discussed before integration into the easy-to-use checklist for the Advised Protocol for OCT Study Terminology and Elements in Rodents (APOSTEL-R) (Table).

Report the Study Protocol

The study protocol includes the number of OCT devices, operating sites, and graders as well as relevant information on the rodent strain as well as detailed reports on any therapeutic interventions and the timelines of the experiment and OCT measurements, which may be reported in accordance with established guidelines for reporting animal experiments such as ARRIVE.[22] In case of limited word count, parts of methodologic protocols may be added as supplementary material.

Report the OCT Device

Commercially available OCT devices vary in their acquisition protocols, optics, and postprocessing algorithms. Thus, it is important to provide details such as device's type, wavelength, manufacturer, and analysis software. Furthermore, and particularly in rodent studies, custom-made imaging devices are often used, which requires additional specifications such as

Table Seven-Point Checklist for the Advised Protocol for OCT Study Terminology and Elements in Rodents (APOSTEL-R)

Item	Category	Recommendation
1	Study protocol	(1) Report how many OCT devices, operating sites, and graders were included
		(2) Report relevant information on the rodent strain (minimum: genetic background including substrain employing internal nomenclature, number of animals, litter mate controls, age, sex)
		(3) Provide detailed reports of any therapeutic interventions tested in rodents, including route of administration, vehicle, and dilution (this is of particular importance for intravitreal injections but should also be reported for intraperitoneal (*i.p.*) and per os (*p.o.*) administrations)
		(4) Report the exact timeline of the OCT measurements (e.g., on which day before/after surgery or treatment, schedule of OCT measurements in case of longitudinal experiments)
		(5) In case of limited word count, consider submitting the exact methodology as supplementary material
2	OCT device	Report the device's type (e.g., time/spectral domain, swept-source, adaptive optics), manufacturer, model, and version. If a custom-made laboratory device is used, the specifications/parameters should be reported along with the software info to analyze the OCT data (e.g., beam diameter, laser power, oversampling rate, wavelength, axial and lateral resolution, adaptive optics)
3	Acquisition settings and modifications	(1) Report on the holder used and/or the bedding/supportive devices (e.g., heat pad) of the rodent during examination
		(2) Report the type, dosage, route, and duration of anesthesia
		(3) Report, if the pupils were dilated before examination (yes/no) and if so, which drug was used
		(4) Report, if eye gel/drops were used for the examination (yes/no) and if so, from which manufacturer
		(5) Report, if a contact lens was used (yes/no), and if so, report the specifications of the used lens
		(6) Report other modifications or setups, if used (e.g., adaptive optics, lenses on the OCT camera)
		(7) Report how perpendicular alignment of the OCT beam on the retinal tissue was assured (e.g., live OCT imaging in vertical and horizontal planes)
4	Scanning protocol	(1) Report the used scan type (e.g., circular scan, volume scan, star scan, line scan, other)
		(2) Report the scan location (e.g., optic nerve head). If automated image-processing approaches are included in the study, report how the optic nerve head location is decided
		(3) Report the scan parameters (with or without eye tracking, follow-up function used) and how you corrected for breathing artifacts. Minimum set of scan parameters: • Volume scans: size of scan area (degrees or area), area location of measurement (degrees or millimeters), number of B scans, spacing between B scans, alignment of B scans, number of A scans per B scan • Radial scans: size of scan area (degrees or line length), number of B scans and/or angle between the 2 adjacent radial B scans, alignment of B scans, number of A scans per B scan • Ring scans: Diameter, number of A scans per B scan, number of B scans averaged for a final B scan, manual or automatic placement of ring • Line scans: Angle, location, number of A scans
5	Fundoscopic imaging	(1) Report on potential other imaging modalities you used in addition to OCT (e.g., fundoscopy, confocal scanning laser ophthalmoscopy, retinal angiography, autofluorescence imaging, electroretinogram)
		(2) Describe the acquisition protocol for all used imaging modalities, including (if applicable): Excitation wavelength, fluorophore (in genetically modified strains), filter sets, number of frames averaged and/or manual z-stack with distance in diopters
		(3) Report device-specific features if utilized (e.g., enhanced depth imaging, swept-source OCT, adaptive optics)
6	Postacquisition data selection and image data analyses	(1) Report how scan quality was assessed, including if and how scans were selected for analysis or discarded providing a detailed description of your quality control criteria
		(2) Report on your postacquisition exclusions (percentage or number and criteria)
		(3) Report, how you selected eyes for analyses (if applicable)
		(4) Report, which software was used for processing scans and for segmentation (might be different from the acquisition software) as well as additional potential postprocessing steps (e.g., denoising)
		(5) Report, which retinal layers were segmented and included
		(6) Report the segmentation method (automated, semiautomated, or manual). Also report, how potential bias was addressed in the case of manual segmentation or manual correction of automated segmentation errors (e.g., blinding of raters)
		(7) Report—if applicable—which grid was used for data extraction (include at least: size, shape, selected sections)
		(8) Report the pixel to millimeter ratio, if images were exported and, if not, how thickness values were obtained from device's proprietary software

Continued

Table Seven-Point Checklist for the Advised Protocol for OCT Study Terminology and Elements in Rodents (APOSTEL-R) *(continued)*

Item	Category	Recommendation
7	Qualitative and quantitative results	(1) Report, which anatomical structures were analyzed (e.g., peripapillary retinal layers), optimally illustrated by an example image or figure
		(2) Report the units of provided measurements (e.g., volume or thickness)
		(3) Report the number of eyes presenting abnormalities on qualitative assessment as well as the abnormalities themselves (e.g., drusen)
		(4) Report the statistical models used for the analyses of OCT data relevant to the control and study design (contralateral/unaffected eye, naïve control group, placebo-treated control group, etc). Also report, whether data were analyzed by eye or by rodent (mean or correcting for within-subject intereye correlations)
		(5) Display individual data of eyes (or mean of both eyes) as single data point in graphs rather than mean values per group
		(6) If relative changes in longitudinal measurements are presented, report how these correspond to absolute values (e.g., volume or thickness of specific layers)

the manufacturer of core components, oversampling rate, and resolution and the type of software algorithm used for OCT-angiography data extraction.

Report the Acquisition Settings and Modifications

OCT measurements in rodent experiments should be performed under standardized conditions including the use of anesthesia, pupil dilatation, and the design of the air-eye interface with eye drops/gels and/or contact lenses/microscopy cover glasses. These conditions should be reported along with descriptions on how the animal was fixated or bedded. Furthermore, additional modifications or setups and other methods to improve acquisitions should be reported, especially how perpendicular alignment of the OCT beam was assured.

Report the Scanning Protocol

OCT scanning protocols may affect resolution as well as morphometric and volumetric results. To reduce acquisition time, some rodent researchers only perform one or 2 scans per eye. Reporting should include all scan types used in the experiment, the exact location of the scan (preferably by showing a funduscopic image indicating the OCT scan area), and how the location was identified (initially and if a follow-up modus was used). For B scans which are off-center, the approximated degree of eccentricity should be provided (either as an angle or as x-times optic nerve head diameter). Detailed scan parameters depending on the scan type, mainly including the (1) scan size; (2) number, direction, and alignment of B scans; and (3) number of A scans per B scan should be reported. In rodents, it is crucial to further report if and how breathing artifacts were minimized.

Report Fundoscopic Imaging

Many rodent OCT studies pursue further fundus imaging modalities or employ other device-specific features such as autofluorescence imaging, confocal scanning laser ophthalmoscopy, retinal angiography, enhanced depth imaging, swept-source OCT, and adaptive optics. If such results are reported, details on these methods and their acquisition protocols should be included with all relevant features (e.g., excitation wavelength, fluorophore in genetically modified strains, filter sets, scanning angle, number of frames averaged, and/or manual z-stack with distance in diopters).

Report Postacquisition Data Selection and Image Data Analyses

Rodent studies should undergo a standardized image selection process, and all inclusion and exclusion criteria for images as well as the number of included and excluded images should be stated. Especially relevant in rodent OCT imaging is a strict image quality check. Although quality control criteria for OCT imaging in humans such as the OSCAR-IB have been published,[8] no standardized quality criteria for rodent OCT imaging currently exist. Thus, employed quality criteria such as cutoffs of signal strength should therefore be reported. Subsequently, images are commonly further processed. The postprocessing is software-specific, and many rodent researchers perform additional steps employing other software options. Intraretinal segmentation for layer quantification is one of the most common types of postprocessing and can be performed by device-specific or custom-made algorithms including artificial intelligence–based options. The authors should report exactly on the software and methods used to postprocess and segment the OCT data. If segmentation was performed manually, it is crucial to report how bias was addressed (e.g., blinding of raters). As results originating from different areas of the retina and different scans are not necessarily comparable, the grid and location of data extraction and the pixel to millimeter ratio should be reported. Common options include sizes based on the grid defined for the Early Treatment of Diabetic Retinopathy Study (ETDRS).[23] Furthermore, it should be clarified how the location/center of the scan was identified (manually/automatically).

Report Qualitative and Quantitative Results

To improve comparability of rodent OCT data, results should be derived and reported in a standardized fashion. This includes clear statements on which results were derived from scans of which anatomic structure and the unit of reported measurements (e.g., volume in mm^3 or thickness in μm) as well as the number of eyes presenting abnormalities on qualitative assessments and the type of these abnormalities (e.g., deposits). Furthermore, the statistical models should be clearly stated, and it has to be clear, whether data were analyzed by rodent (mean of both eyes) or by eye. In the latter case, the model must correct for within-subject intereye dependencies. In graphs, individual data of eyes (or mean of both eyes) should be represented as single data points instead of plotting the group means. If relative longitudinal changes are reported, it should be clear how they correspond to absolute values.

Discussion

The APOSTEL-R recommendations aim to guide researchers in reporting their rodent OCT data consistently and conclusively allowing other scientists, reviewers, and editors to compare studies and evaluate outcomes across studies. Rather than a rigid layout, it is meant as a suggestion and guide throughout the experimental process from initial stages of study design to the published manuscript. Adhering to the APOSTEL-R recommendation may help to avoid common pitfalls and might support other researchers in reducing their animal numbers or refining their experiments in accordance with the 3R principle by providing comparable and reproducible results.[24]

As formal evidence on the impact of our recommendations on rodent OCT data quality and results is missing, a meta-analysis or comprehensive review is currently not possible. Thus, these recommendations are class IV evidence and solely based on the experience of researchers with proficiency in running, analyzing, reporting, and reviewing rodent OCT studies. As the field is still rather small, the number of participants was limited and possibly influenced by the network and collaborations of the expert panel. Yet, considering the variety of existing rodent OCT studies and the heterogeneity in opinion, this consensus and subsequent standardization is a first step toward a refinement of these recommendations with an increased level of evidence. In addition, subsequent work should incorporate guidance on quality control of rodent OCT data.

The APOSTEL-R recommendations are an expert consensus statement to improve the quality and comparability of retinal OCT studies in rodents. As OCT technology and rodent research develops, and as further evidence accumulate, further refinement will be necessary.

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Appendix Coinvestigators

Coinvestigators are listed at Neurology.org/NN.

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