Requirement of age-dependent normalization of spectral-domain optical coherent tomography parameters in non-human primates for translational studies

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The systematic use of spectral-domain optical coherent tomography (SD-OCT) and OCT angiography (OCTA) in the assessment of human inherited retinal diseases and glaucomas is providing novel valuable informations susceptible to improve our understanding of the pathophysiology of these diseases [1] and their treatment. There is an absolute necessity to test novel therapies for these diseases in animal models before the implementation of any possible clinical trial in human patients. The closest animal models of most human genetic diseases, and particularly ocular diseases, are non-human primates (NHP). Macaques, such as *Macaca fascicularis* (cynomolgus macaque) and *Macaca mulatta* (rhesus macaque), have been extensively used in the field of experimental ophthalmology since the size of their eyes and their structures allow an easy adaptation of clinical imaging technologies used in human patients: color fundus photography (CFP), fundus autofluorescence (FAF), fluorescein angiography (FA), and indocyanine green angiography (ICGA), multimodal imaging modalities including spectral-domain optical coherence tomography (SD-OCT), near-infrared reflectance (NIR) imaging, and OCTA. Since 2014, genome editing in NHP became an efficient method for generating monkey models using transcription activator–like endonucleases (TALENs) or clustered regularly interspaced short palindromic repeats (CRISPR/Cas9). Some of these NHP models displayed clinical manifestations that were much closer to those of human diseases than those previously observed in mouse models [2]. NHP models have been successfully obtained, using these technologies, for Huntington disease and Rett syndrome, spino-cerebellar

ataxia 3 (SCA3), and Duchenne muscular dystrophy (DMD). Despite the fact that canine models of many human inherited retinal dystrophies are available, characterized clinically, and have served for validating several gene therapies, obviously, NHP models of human inherited retinal dystrophies will be obtained very soon in order to increase the efficacy of pharmacological, gene, and cell therapies in sick human patients waiting for reliable cures. The observation of the closest clinical manifestations of these human diseases in the novel NHP models requires the determination of the normal images obtained especially by SD-OCT, near-infrared reflectance (NIR) imaging, and OCTA in normal NHP primates throughout their lifespan. Very recently, the accurate parameters of the images obtained by SD-OCT for the macular area of adult *Macaca mulatta* have been definitively validated [3]. SD-OCT images of the retina and choroid evolve in monkeys since birth to geriatric ages. A recent report of results of enhanced depth imaging (EDI) OCT showed the visualization in non-infant *Macaca fascicularis* four hyper-reflective micro-layers in the outer retina: the external limiting membrane (ELM), the ellipsoid zone (EZ), the interdigitation zone (IZ), and the RPE; whereas the IZ could not be detected in infant *Macaca fascicularis* [4]. Furthermore, NIR and SD-OCT allowed to detect choroidal vessels in non-infant macaques with certainty, whereas they were not detected or much more difficult to detect in infant macaques. Importantly, this study of healthy *Macaca fascicularis* confirmed results, previously obtained by SD-OCT in healthy rhesus macaque, demonstrating the ill-definition of the choroidal-scleral junction (CSJ) and the existence of a well-delineated choriocapillaris (CC) layer. This report revealed that the choroid has a very different appearance in macaques compared to that in humans. The measurement of choroidal thickness is only reliable and repeatable when a clear CSJ is observed. Of utmost importance, this report emphasizes the fact that, to date, the measurement of choroidal thickness using EDI SD-OCT in non-infant macaques is still impractical and provides with a very high

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probability false data [4]. For the future studies of inherited chorio-retinal dystrophies occurring at early stages in the novel NHP models, this observation should be taken into account seriously. This study confirms that the choroid of most macaques has a clearly delineated, hypo-reflective choriocapillaris layer. This well-delineated CC layer observed in macaques might be altered in diverse disorders such as choroidal neovascular age macular degeneration, diabetic retinopathy, and genetically induced glaucoma, with the novel gene editing technologies in NHP. The necessity to determine the genuine parameters of images obtained by SD-OCT throughout the life is further supported by two recent studies. The first study demonstrates, by SD-OCT measurements, that over the first 18 months of *Macaca mulatta* life, the mean retinal thickness at the pit center of the developing fovea increased by 21.4% with a corresponding 20.3% decrease in pit depth. The major changes occurred within the first 120 postnatal days. They did not stabilize until a year after birth [5]. These observations are of great consequence for the evaluation by SD-OCT of very early-onset cone and cone dystrophies. The second study demonstrated, by a SD-OCT follow-up monitoring of an early experimental glaucoma (EG), that, at similar postlaser times, levels of cumulative intra-ocular pressure (IOP) insult and axonal damage, SD-OCT-detected optic nerve head (ONH) connective tissue structural change was greater in young compared with old monkey EG eyes [6]. This significant observation supports greatly the necessity to perform longitudinal studies both for normal and sick macaques, especially when multimodal imaging is performed. This report does take into account the advances provided by OCT angiography, which allows the visualization of retinal and choroidal capillary networks as never before. OCTA has already been used in macaques affected by an experimental glaucoma and allowed to discover that, around the ONH, the inner retinal capillary density gradually decreased with increasing IOP, reaching statistical significance when pressure

exceeded 50 mmHg, but returned when IOP was reduced [7]. Complementary experiments using OCTA are required for refining the conclusions stated in the recent report discussed here [4].

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