Structure-Function Analysis of MP-3 Microperimetry versus Octopus Perimetry in Central Glaucomatous Visual Field Defects

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Abstract
Introduction: The aim of this study was to compare the structure-function relationship with microperimetry and Octopus perimetry in primary open-angle glaucoma (POAG) patients with central visual field (VF) defects. Methods: Forty eyes of 24 patients with POAG were enrolled. Circumpapillary retinal nerve fiber layer (cpRNFL) analysis measured by spectral-domain optical coherence tomography (SD-OCT) of the superotemporal, temporal, and inferotemporal optic-nerve head sectors were related to corresponding microperimetric and Octopus VF clusters using the G2 grid-pattern with dynamic strategy, respectively. The structure-function relationships of both devices were assessed via a segmented regression, as well as linear regression across overall SD-OCT cpRNFL values and outside normative (<1%) SD-OCT cpRNFL values. Results: Linear and segmented regression fits were similar with both devices. Across overall cpRNFL sectorial values, structure-function relations for the superotemporal, temporal, and inferotemporal optic-nerve head sectors were $R^2 = 0.176$ ($p < 0.001$), $R^2 = 0.008$ ($p = 0.069$), and $R^2 = 0.294$ ($p < 0.001$) for microperimetry and $R^2 = 0.189$ ($p < 0.001$), $R^2 = 0.020$ ($p = 0.002$), and $R^2 = 0.326$ ($p < 0.001$) for Octopus perimetry. For corresponding values outside normative limits (<1%), the relationships were $R^2 = 0.113$ ($p < 0.001$), $R^2 = 0.001$ ($p = 0.836$), and $R^2 = 0.420$ ($p < 0.001$) for microperimetry and $R^2 = 0.192$ ($p < 0.001$), $R^2 = 0.002$ ($p = 0.336$), and $R^2 = 0.366$ ($p < 0.001$) for Octopus perimetry. Discussion/Conclusion: Structure-function analysis was similar for both devices. Fundus-tracking should be further evaluated in a longitudinal setting in patients affected by glaucoma.

Introduction

Primary open-angle glaucoma (POAG) belongs to a set of chronic diseases that lead to optic neuropathy with pathological structural and functional changes, which if left untreated, can potentially lead to bilateral blindness [1]. Both structural and functional changes are the result of premature irreversible retinal ganglion cell apoptosis, causing pathognomic changes of the optic-nerve head (ONH), such as thinning of the retinal nerve fiber layer.
(RNFL), progressive loss of neuroretinal rim, and optic-disc cupping. Measurements of RNFL thickness with spectral-domain optical coherence tomography (SD-OCT) can be achieved with high precision [2], with implemented normative data bases to classify the amount of premature structural damage in accordance with the topographic arrangement of nerve fibers entering the ONH. Therefore, structure-function mapping between structural damage in defined ONH sectors and their respective visual field (VF) portions is possible [3, 4].

Nevertheless, this relationship has only led to moderate correlations, a limitation partly attributable to the functional domain, where standard automated perimetry (SAP) as the gold standard is a psychophysical procedure that relies on patient compliance for diagnostic sensitivity. This is affected by sources of noise such as learning effects, fatigue effects, and patients’ fixation stability [5].

Microperimetry is a VF examination with fundus-oriented real-time fundus-tracking control, whereby stimuli instead of being back-reflected from a spherical cupula, as in SAP, are directly projected onto retinal regions of interest. This premise lent itself predominantly for investigations in patients with macular diseases with lost central vision [6–8]. However, the prospect to be able to project stimuli at preplanned locations for follow-up examinations and the possibility to largely eliminate measurement noise due to fixation instability have also been of interest for glaucoma patients [9, 10]. The MP-3 microperimeter is a device (NIDEK Co., Ltd., Aichi, Japan) with a larger dynamic range than its predecessor, the MP-1, which facilitates a clinical application in patients affected by glaucoma because a more interrelated comparison between SAP is possible [11–13]. The main limitation of the MP-3 microperimeter is however the reduced VF angle, which by virtue of being able to only cover the central 20° VF portion, would primarily result for a diagnostic application in patients with central glaucomatous damage – where VFs become unreliable due to a marked increase in measurement variability.

The fact that real-time fundus-tracking could be able to neutralize grid-pattern shifts and account for perimetric measurement noise due to fixation instability can be insofar relevant is because the presence of glaucomatous damage is known to have a detrimental impact on this reliability criterion [14]. This can be already affected by early glaucomatous damage causing central VF defects [15] – with microperimetry having shown to be able to detect initial central VF dysfunction that may not be identifiable with SAP [16]. Since progressive localized RNFL thickness reduction in areas prone to glaucomatous damage is most frequently detected [17], and the decision for surgical intervention is sometimes based on central VF deterioration, the aim of the present study was to comparatively evaluate sectoral structure-function relationships of temporal RNFL zones between microperimetry and conventional SAP (Octopus, Haag-Streit AG, Germany) in POAG patients.

Materials and Methods

Patients

Inclusion criteria were 21 years of age or older with preexisting POAG associated changes as well as a mandatory glaucomatous VF defect in one or both eyes defined as having >2 dB mean deviation, a loss of variance of >6 dB, as well as >7 points decreased by >5 dB within the central 20°, of whom which 3 were contiguous. After a complete ophthalmic examination including slit-lamp biomicroscopy, IOP measurement, and funduscopy, the same investigator provided all participants with identical instructions for perimetric assessments. Excluding criteria were any presence of ocular media opacities, pregnancy, other types of glaucoma, VF defects due to other diseases, and refractive error outside ±5 diopter spherical equivalent. When both eyes of a patient met the inclusion criteria of manifest glaucomatous VF manifestation in the central 20°, both were included. Perimetric examinations were performed with the MP-3 microperimeter and the Octopus 101 (Haag-Streit AG, Germany) on the same day. All study-related documents were reviewed by the Ethics Committee of the city of Vienna, and written informed consent was obtained in all patients prior to study entry. The study followed the guidelines of Good Clinical Practice and adhered to the Tenets of the Declaration of Helsinki.

Spectral-Domain OCT

SD-OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) RNFL thickness measurements were performed for each patient on the same day as perimetric measurements. The circumpapillary RNFL (cpRNFL) thickness was measured over a circle diameter of 12.0° (3.5 mm) by averaging 100 cross-sectional images. The ONH is subdivided by the Spectralis algorithm to quantify the RNFL thickness along the circular scan in accordance with patients’ fovea-to-disc axis into six 12 clock-hour sectors, which are stratified with respect to the age corrected normative database [18] as either within 95% of referential measurements (within normative limits), thinner than the reference database range at the 5% level (possibly outside normative limits), or 1% level (outside normative limits). Since the microperimetric VF radius only covers the central 20° of eccentricity, only VF areas covered by the angles of both perimetric devices were related to their respective ONH sectors, namely the sectors 45°–90° (temporal superior ONH; inferior arcuate VF cluster), 315°–45° (temporal ONH; central VF cluster), and 270°–315° (temporal inferior ONH; superior arcuate VF cluster). Any images with improper ONH visualization or measurement failure that did not meet the quality index recommended by the manufacturer were discarded.
**MP-3 Microperimetry**

The MP-3 microperimeter is a perimeter with an automated fundus camera covering a 20° VF angle. It has a maximum stimulus intensity of 10,000 asb, a background luminance of 31.4 asb, a dynamic range of 0–34 dB, as well as Goldman compatible stimulus size selection. Prior to measurements, an LED lamp captures a referential infrared image of the retina to generate landmark regions. On that basis, horizontal and vertical shifts of patients’ fixation are registered and compensated at 30 frames per second in real time to enable precise projection of stimuli at predefined positions. At the end of the examination, the built-in CCD camera captures a color image of the fundus to visualize topographical alignment.

**Perimetric Testing Protocol**

Patients were measured with their contralateral eye patched in a dark quiet room with ambient illumination less than 1 lux. For this study, the Octopus G2 grid-pattern [19] with dynamic strategy and 4-2 staircase bracketing was chosen. The pattern consists of 59 stimulus locations in the 30° VF area along with a high density in the central portion at a spacing of 2.8° that relate physiologically to the arrangement of nerve fiber bundles. The customizable microperimetric pattern editor was used to recreate the Octopus G2 program, and a white light with a stimulus size of 25.7 arc minutes and with a visual angle of 0.428° (Goldman III) as well as a stimulus duration of 100 ms was used for both devices to comparatively evaluate VF examinations. Although the included glaucoma patients had great experience in performing VFs, to reduce the possibility of a learning effect, two measurements on separate days were performed with both devices prior to the measurements used for statistical analysis. The sequence of measurement was randomized with an adequate in-between breaktime. Although the MP-3 is labeled by the manufacturer as having a nonmydriatic fundus camera, in the case of automatic pupil alignment not being feasible, mydriatic tropicamide eyedrops (Mydriatikum Agepha; Agepha, Vienna, Austria) were used for pupil dilation, and in case automated fundus alignment was not possible, two landmark points at crossing retinal vessels were manually registered. Only VFs with reliable fixation indices were used for comparison.

**Statistical Analysis**

With 31 of 59 testing points covered by the 20° VF radiuses of both devices, pointwise threshold sensitivities were related based on the structure-function mapping method by Garway-Heath et al. [4] to temporal ONH portions as defined by the cpRNFL thickness plot of the Spectralis software. Thereby, test loci of respective G2 grid-pattern clusters with dynamic strategy were related to the 315–45°, 270–315°, and 45–90° sectors for comparative statistical analysis. For the sake of readability, the aforementioned regions are referred to as the superotemporal (45–90°), temporal (315–45°), and inferotemporal (270–315°) ONH sectors throughout this paper, which correspond to the lower arcuate, temporal, and upper arcuate VF clusters, respectively, shown in Figure 1.

Since eyes within patients are intercorrelated, a nested statistical model was used to include both eyes, where each eye was nest-
ed within patient. The Shapiro-Wilk test was used to assess the normality of variable distribution, and parametric statistics for testing a hypothesis were only used if the assumption of normality was met. Parameters were represented by descriptive statistics with means and standard deviations (±) for normally distributed variables and median and first and third interquartile for nonnormally distributed variables.

Because contrast sensitivity of polychromatic perimetric stimuli is by convention expressed in decibels (dB), and a 1-dB drop represents a change of 0.1 log10 units of light attenuation (this unit being reciprocal of the unit of stimulus luminance in cd/m²), measurement values of both devices were linearly scaled, before being averaged and reconverted to logarithmic scaling via following formula [20]:

\[
\frac{1}{\text{Lambert}} = (10)^{0.1 \times \text{dB}}.
\]

Measured mean sensitivity (MS) values of MP-3 microperimetry and Octopus perimetry were regressed against each other to establish correlation coefficients. To investigate the plateauing of MS values and their decline as a function of cpRNFL thickness for each device, two models were fitted to the data. To comparatively evaluate how both devices delineate glaucomatous VF deterioration in each sector, a segmented regression was fitted to the data. As such, the segmented model enables the assessment as to how structural changes measured by SD-OCT relate to tipping points at which VF deterioration is to be expected as measured with both perimetric methods. To do so, the Davies test [21] was used to provide an initial value that was used as the starting point to fit a segmented regression with an unknown breakpoint for each of the sectors [22]. Thereby, the segmented breaking points between both perimetric devices and RNFL thickness values were evaluated along with respective 95% confidence intervals. Additionally, a locally weighted scatterplot smoothing curve [23] was fitted which combines least squares regression and nonlinear regression to use subsets of neighboring data points for generating localized models. As such, without having to define a priori a function, a fit can be generated for the designated sample.

Lastly, a linear regression was further employed to assess the structure-function relationship between threshold sensitivity of each device and cpRNFL sectors. This was performed across all values, as well as below the SD-OCT delineation for outside normative values (<1%) in respective sectors. The reason being is that the perimetric examination for more depressed VFs becomes more difficult due to an intermingled combination of factors such as unreliable indices [14] and fixation loss [5]. Outcome values were expressed as \(R^2\). All data analyses were conducted with SPSS statistics for MAC software (version 26.0. International Business Machine Corp) and the programming language R v. 3.6.1 (www.r-project.org).

Results

Forty eyes (20 OD, 20 OS) of 24 patients with POAG that met inclusion and exclusion criteria in one of both eyes were enrolled in this monocenter study from the
glaucoma outpatients’ department. Patient demographics are shown in Table 1. In 1 subject, automated pupil alignment was not feasible with the fundus camera of the microperimeter, whereby in that case, measurements with both devices had to be conducted after pharmacological pupil mydriasis.

**Retinal Sensitivity Values**

Perimetric values were not normally distributed \( (p < 0.05; \text{Shapiro-Wilk test}) \), and a statistically significant difference for all three sectors was observed between both devices \( (p < 0.001, \text{paired Wilcoxon test}) \). For Octopus perimetry, median values of the superotemporal, temporal, and inferotemporal ONH sectors were 27.20 (3.10–30.40), 28.77 (8.91–31.82), and 23.15 (0.00–29.90), respectively. Correspondingly, median MP-3 values were 23.95 (2.10–27.20), 24.91 (1.82–28.09), and 21.30 (0.00–26.50), respectively. Correlation coefficients between the two devices for the superotemporal, temporal, and inferotemporal ONH sectors were 0.902 \( (p < 0.001) \), 0.867, \( (p < 0.001) \), and 0.943 \( (p < 0.001) \), respectively, shown in Figure 2.

**Segmented Fit**

The segmented regression for the superotemporal ONH sector showed similar breakpoints for both devices, with Octopus perimetry at 96.26 μm (95% CI: 72.2–120.3; \( p < 0.04 \)) and MP-3 at 98.7 μm (95% CI: 58.6–138.8; \( p < 0.08 \)), although the latter was borderline significant shown in Table 2. For the temporal ONH sector, the hypothesis of an existing breakpoint was rejected for both devices (Octopus: \( p = 0.69 \); MP-3: \( p = 0.70 \)). The segmentation of the inferotemporal ONH sector however was highly significant for the Octopus at 63 μm (95% CI: 50.3–75.4; \( p < 0.001 \)) and MP-3 at 68.15 μm (95% CI: 57.3–79; \( p < 0.001 \)), with a functional lag behind the age-corrected SD-OCT delineation of abnormal limits at \( \sim 93 \mu m \).

**Linear Regression Analysis**

Table 3 shows a comparative structure-function evaluation between MP-3 microperimetry and Octopus perimetry for overall measured VF sensitivity and VF measured in sectors outside normative limits (<1%). The overall structure-function relationships for the superotemporal, temporal, and inferotemporal ONH sectors were \( R^2 = 0.176 \) \( (p < 0.001) \), \( R^2 = 0.008 \) \( (p = 0.07) \), and \( R^2 = 0.294 \) \( (p < 0.001) \) for microperimetry and \( R^2 = 0.189 \) \( (p < 0.001) \), \( R^2 = 0.002 \) \( (p = 0.83) \), and \( R^2 = 0.326 \) \( (p < 0.001) \) for Octopus perimetry, respectively. Analogously, values outside cpRNFL normative limits (<1%) were \( R^2 = 0.113 \) \( (p < 0.001) \), \( R^2 = 0.001 \) \( (p = 0.83) \), and \( R^2 = 0.420 \) \( (p < 0.001) \) for microperimetry and \( R^2 = 0.192 \) \( (p < 0.001) \), \( R^2 = 0.002 \) \( (p = 0.33) \), and \( R^2 = 0.366 \) \( (p < 0.001) \) for Octopus perimetry, respectively.

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**Table 2.** Segmented regression fit with breaking points for each of the perimetric methods

| Parameter (40 eyes of 24 patients) (95% CI) | Octopus perimetry | MP-3 microperimetry |
|--------------------------------------------|-------------------|---------------------|
| Superotemporal ONH sector, μm              | 96.26 (72.2–120.3)* | 98.7 (58.6–138.8)   |
| Temporal ONH sector, μm                    | NA                | NA                  |
| Inferotemporal ONH sector, μm              | 63 (50.3–75.4)**  | 68.15 (57.3–79)**   |

Segmented regression: * \( p < 0.05 \); ** \( p < 0.001 \).

**Table 3.** Comparative structure-function analysis

|                             | Octopus perimetry | MP-3 microperimetry |
|-----------------------------|-------------------|---------------------|
| cpRNFL overall \( R^2 \)    | \( p \) value     | \( R^2 \) \( p \) value |
| Superotemporal ONH sector   | 0.189 \( <0.001 \) | 0.176 \( <0.001 \)   |
| Temporal ONH sector         | 0.020 \( 0.002 \)  | 0.008 \( 0.069 \)    |
| Inferotemporal ONH sector   | 0.326 \( <0.001 \) | 0.294 \( <0.001 \)   |
| Outside normative cpRNFL limits (<1%) | | |
| Superotemporal ONH sector   | 0.192 \( <0.001 \) | 0.113 \( <0.001 \)   |
| Temporal ONH sector         | 0.002 \( 0.336 \)  | 0.001 \( 0.836 \)    |
| Inferotemporal ONH sector   | 0.366 \( <0.001 \) | 0.420 \( <0.001 \)   |
Discussion/Conclusion

To the best of our knowledge, this is the first study to evaluate the structure-function relationship with MP-3 microperimetry in comparison with Octopus perimetry. We found a high agreement between average MS values in respective sectors between both devices, and as previous authors have already noted in a comparative analysis with the Humphrey Field Analyzer [12], a statistically lower sensitivity of ~3 dB for MP-3 microperimetry was observable. This could be explained by the different dynamic ranges of both perimeters, as well as their fundamentally different methodologies.

Previous retrospective cross-sectional studies have evaluated sectoral tipping points with SAP [24, 25], where the amount of structural loss that needs to be present to be able to expect detectable clinical functional loss in defined RNFL sectors had been estimated. In our study, the si-
laries for both devices of the segmented fit (breaking points in the regression) and the local smoothing curve might indicate that real-time fundus-tracking, at least with the spacing of the G2 grid-pattern with dynamic strategy, would not translate into a higher sensitivity for earlier scotoma detection than Octopus perimetry (see Fig. 3). Since patients with suspected glaucoma were not part of the study protocol, these estimated breakpoints should not be applied for interindividual clinical application and were solely used for comparative analysis with respect to cutoff values at which the slope in the regression would mark a steep decrease for each of the devices. It is further worth noting that for the temporal sector (central VF region), no segmented regression was possible with both devices. This, along with the observable and known floor effect of structural SD-OCT measurements, reemphasizes the importance of reliable functional VF examinations with respect to central vision in later stages because in advanced glaucoma, a small decrease in MS can lead to substantial deterioration in patients’ visual function.

With linear regression, the inferotemporal ONH sector had a tighter structure-function relation for both perimetric devices, while the superotemporal ONH sector showcased a weaker and the temporal portion weak/no correlation. For data outside normative <1% SD-OCT limits, the MP-3 had a somewhat tighter relationship for the inferotemporal ONH sector as shown in Table 3. One possible reason for this finding is that in our study population, glaucomatous damage was more advanced in the superior arcuate VF cluster (Bjerrums’ area), i.e., the cluster most affected by POAG. This could indicate that the benefit of continuous eye tracking for precise stimulation of test loci could primarily come to fruition with respect to increasing fluctuations as a function of moderate to advanced localized VF deterioration. Conventional perimetry uses the Heijl and Krakau method [26], whereby stimuli are periodically projected onto the blind spot to assess fixation stability, thus relying on the assumption that there is an absence of topographic ONH variations and/or positioning. This will however not be the case when grid-pattern misalignments occur because they can impact the validity of reliability indices by artificially increasing false-negative results and fluctuation, as well as most importantly, potentially lead to an overestimation of threshold values and thus possibly blur out deep scotomas [27]. In patients with high myopia, for example, the deviation of the ONH position can make the assessment of fixation stability with SAP by periodic projection of stimuli onto the blind spot challenging. Additionally, the manual positioning of trial lenses to adequately correct for refractive error also needs to factor in vertex distance precision, which can amplify intra-/interobserver variability. In contrast, the MP-3 has a built-in optical apparatus that can automatically adjust the focus on the retina (range: −12 to +15 D).

In general, however, the primary limitation of MP-3 microperimetry for glaucoma detection is the limited VF angle, especially in light of the fact that peripheral test points are known to be harder to reproduce [28], and glaucomatous changes usually first occur there [29]. Its main application for patients with glaucoma would therefore be for longitudinal functional analysis of central VF defects. The fact that microperimetric real-time fundus-tracking control could reduce sources of variability due to fixation instability and enable the projection of stimuli at pre-planned locations is as a premise insofar interesting because similarly to SD-OCT in the structural domain, the procedure offers a follow-up mechanism in the functional domain. The projection of stimuli at predefined locations with continuous real-time alignment would therefore lend itself for corresponding functional fovea-to-disc axis orientation. This could be important because for SD-OCT, the improved correspondence of ONH segments with topographical optic disc positioning has shown to enhance the follow-up function in a longitudinal setting [30].

In our previous recent study, the MP-3 microperimeter showed a higher reproducibility than the Octopus perimeter across three different visits [13], while Tepelus et al. [31] recently showed that MP-3 retinal sensitivity values were also well-correlated with those of the Humphrey Field Analyzer in patients affected by low-tension glaucoma. Since structure-function analysis does not necessarily indicate diagnostic utility per se [32] and currently a minimum of 7–8 VF examinations are required for adequate sensitivity and specificity [33], a next step will be to evaluate microperimetry in a longitudinal setting to assess its potential for a more intertwined progression analysis than conventional perimetry. This can be insofar interesting because it is known that (a) eyes have anatomical variations in nerve fiber count [34], (b) the Spectralis SD-OCT uses a dual-beam technology to compensate for eye motions and take into account patients’ fovea-to-disc axis orientations (range in the present study: −17.9 to 10.9°), and (c) customization of ONH mapping with individual sectors has shown to improve correlations and thus potentially unmask localized functional loss [35]. For the latter, microperimetric progression analysis could also further itself in conjunction with functional OCT extensions such as polarization sensitive OCT that are able to account for interindividual structural retinal nerve fiber bundle arrangements [36]. This could be used to fur-
ther exploit fundus-related microperimetry for its potential to facilitate the intertwining of structural OCT measurements in a longitudinal setting.

For the present study, some limitations are worth addressing. First, at the time of our investigation, the microperimeter had not an implemented normative database so that only MS values between both devices were compared. Second, while the G2 grid-pattern with dynamic strategy was selected because it is in accordance with the functionality of nerve fiber bundles and enables without an increase in investigation time a reasonable compromise for assessing central and peripheral VFs up to 30° [19], a grid-pattern with tighter spatial mapping would have likely benefited the real-time tracking function of microperimetry. This is especially crucial for VF measurements of patients with respect to initial onset of glaucomatous macular damage, as well as monitoring central VF progression. However, a tighter spacing with more testing loci would have prolonged the microperimetric procedure at the risk of creating fatigue effects, which would have been further amplified in patients with less stable fixation. This highlights the additional limitation of having evaluated only patients with reliable perimetric indices. The potential benefit of real-time tracking at 30 times per second would therefore also warrant further elucidation with faster tendency-oriented threshold algorithms, in order to assess its benefit with respect to the trade-off between intra-measurement fatigue effects and grid spatial mapping.

Based on our findings, Octopus perimetry and MP-3 microperimetry values are well-correlated, and structure-function analysis for both methods is similar. Microperimetric fundus-tracking along with its follow-up function should be assessed in patients affected by glaucoma in a longitudinal setting to fully analyze its potential benefit.

**Statement of Ethics**

All research and measurements followed the tenets of the Declaration of Helsinki and were approved by the ethical review board of the local Ethics Committee of the city of Vienna (approval reference number EK14-251-0515). Written informed consent was obtained from all patients before enrollment in the study and before any study measures were performed. The study was registered at clinicaltrials.gov (https://clinicaltrials.gov) with the clinical trial registration number NCT03365245.

**Conflict of Interest Statement**

O. Findl is a scientific advisor to Alcon, Croma, Carl Zeiss Meditec AG, Johnson & Johnson, and Merck; N. Hirnschall has a research contract with Carl Zeiss Meditec AG and Hoya, but both do not have any financial interests related to the study. The authors have no proprietary or financial interest in any of the materials or equipment mentioned in this study.

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**Author Contributions**

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(1conception of the study, 2data acquisition, 3statistical analysis, 4preparation of the manuscript, 5critical review and final approval of the manuscript).

**Data Availability Statement**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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