Asymmetry in Retinal Properties of Image *'Delivery'* and Perceptual Processing in the Visual Cortices in MS: The Pulfrich Phenomenon

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ABSTRACT:

Background: The Pulfrich Phenomenon (PF) describes a problem patient report in everyday live as a confusion with accurately seeing movement in depth. The PF is the illusory perception that an object moving linearly along a 2-D plane appears to instead follow an elliptical 3-D trajectory. We have designed an objective method to identify the magnitude and direction of the PF in MS patients, and to quantitate its magnitude by abolishing the effect via monocular application of neutral density filters to the less affected eye. We were also able to produce and measure the phenomenon in a control group through the application of neutral density filters to one eye.

Methods: Subjects were asked to indicate whether movement of a linearly moving pendulum followed a 2D (i.e. a linear motion across the frontal plane in front of the patient; which constituted the pendulum's actual motion as elicited by the investigators) versus a 3D elliptical object-motion trajectory.

Results: PF scores increased across MS patients who perceived the phenomenon, and there was a corresponding increase in the magnitude of neutral density filtering necessary to abolish the illusion of elliptical motion ($p<0.001$).

Interpretation: The identification, objective characterization, and corresponding elimination with filtering (or in response to restorative neurotherapeutic agents) of the PF, has potential dividends upon patient safety (e.g. driving), work performance and quality of life. Further, characterization of the inter-eye asymmetry in image detection in the visual cortex may allow for detection and monitoring of central adaptation, therapeutic targeted plasticity, and responses to MS treatments with protective, preventative and restorative neurotherapeutic properties.

Many patients but not all doctors are aware of a disabling problem with accurate perception of movement in depth. In road traffic cars and cycles appear to overtake each other or be at risk for a crash, push bikes appear to be on a head collision course; all leading to a patients confusion. In sports such as lawn tennis, table tennis, badminton, patients cannot any more accurately target the approaching ball. At home, restaurant or kitchen, patients easily spill a drink, milk or liquids if attempting to pour them into a glass. All of this renders patients less confident, decreased their quality of live and can be explained by one unifying mechanism.

The Pulfrich phenomenon (PF) is a visual illusion secondary to a derangement that reflects a relevant asymmetry in the transmission characteristics (or at least in the perceptual image detection) of visual information from the eyes to their ultimate target within the cortices of the parieto-occipital visual processing networks.[1-3] The PF is the illusion that occurs when an object moving linearly along a 2-D plane (e.g. a ball attached to the end of a string fixed at the ceiling and accelerated along a pendular trajectory, where the motion can be described as moving along the horizontal ('x') and vertical ('y') planes) is perceived by the subject to exhibit instead an elliptical 3-D trajectory, that recurrently oscillates through illusory phases of object motion with respect to the actual plane and vector of motion [Figures 1,2].

During one phase the pendulum ball appears to move in front of the actual line of motion, and is perceived to be in closer proximity to the patient than the actual image of the object. Alternately, the second phase of the ball's motion is perceived to be moving behind the actual plane of motion, and thereby appears to be further away from the viewing patient. The mechanism responsible for producing the PF is hypothesized to reflect an inter-eye discrepancy in the electrical transmission properties along the circuitry of the various processing elements from the retina to the visual cortex, as a consequence of asymmetric damage to the visual system (e.g. acute optic neuritis; AON),[1-6] and may reflect the failure of a centrally adaptive set of mechanisms, that would otherwise be triggered in the context of an inter-eye timing discrepancy within the afferent visual network.[7,8]

Cortical neurons (binocular convergence), likely work on spatial characteristics rather than purely on the basis of timing mechanisms.[9,10] Presumably, these neurons sample constantly, within a time window; if a signal is temporally dispersed, the spatial characteristics likewise may change, culminating in a delay in axonal transmission properties to the cortex.[11] This cortical processing of the visual object information thus becomes dissociated, with a delayed signal emanating from the more affected eye.

The objective of our investigation into this phenomenon was aimed at understanding the pathobiological mechanisms underlying delivery of visual object information to the visual cortices. Specifically, what are the consequences of a disparity between the two eyes, such as may be caused by optic neuritis from multiple sclerosis (MS) and its related demyelination.

It has been suggested that vision, and the myriad of pathways involved in its processing, are affiliated with at least half of the brain's networks.[12] The high predilection for MS to target visual networks translates into pathophysiologic alterations, which compromise information concerning the characteristics of object motion in three dimensional space.

The central processing errors that give rise to the PF, have potential implications for safety (in road traffic or operating dangerous equipment), performance in sporting events that are contingent upon the accurate identification of a dynamically moving object's position, speed, and trajectory in visual space, and for other facets of quality of life that are dependent upon vision in general [Figure 3].[13]

Our principal specific aim of the investigations contained herein, was to develop an objective method by which to identify, induce, mitigate or even abolish the PF. Further, we sought to correspondingly measure the magnitude of the PF in MS patients; including those with and without a history of acute optic neuritis (either of which may harbor damage, sufficient to result in a fundamental disparity in the temporal characteristics of image detection within the processing apparatus of the visual cortex). Most importantly, we underscore how such information can be translated into effective, non-invasive, and individualized treatment intervention that is specifically aimed at abolishing this visual system illusion, via the application of graduated (i.e. a systematic titration until the PF is neutralized), neutral density filtering (G-NDF) to the less affected eye, during a linear swinging pendulum ball paradigm (the gold standard method by which the phenomenon objectively corroborates the patient's illusory perception that a linear moving object (along both the 'x' and 'y' axes) appears to instead follow a 3 dimensional trajectory [Figure 4].[3-6,13-15]

METHODS

Study Participants

Thirty-three subjects participated in the study, consisting of ten healthy controls and 23 patients carrying a diagnosis of multiple sclerosis (MS), as defined by the modified McDonald diagnostic criteria [Table 1].[16] All MS patients had a documented history of AON (n=20 unilateral, n = 2 bilateral), with the exception of one patient who was characterized as having unilateral subclinical optic neuropathy, without either recollection of experiencing features suggestive of AON, nor with any medical record documentation of the occurrence of such an event. All testing was performed during a single study visit. Subjects were screened based on their Random Dot Stereo Acuity Test (Vision Assessment Corporation, IL, USA) scores. Stereovision is critical for experience of the PF,[1,3] and therefore any individuals with a history of amblyopia or those who could not perceive at least 400 seconds of arc were excluded from the study.

Standard Protocol Approval, Registrations, and Patient Consents

All participants provided informed and written consent prior to the beginning of the study procedures. Consent was obtained according to the Declaration of Helsinki. The protocol was approved in advance by the Institutional Review Board, of the University of Texas Southwestern School of Medicine.

Visual System Assessments

Stereo Acuity

Subjects were screened based on their Random Dot Stereo Acuity Test (Vision Assessment Corporation, IL, USA) scores. Stereovision is critical for experience of the PF[1,3] and therefore any individuals that could not perceive at least 400 seconds of arc would have been excluded from the study (there were no exclusions as all study subjects fulfilled this criteria.

Visual Acuity/Summation

Subjects were assessed using the low contrast letter acuity charts (2.5% contrast; LCLA). The presence of binocular summation (BS) was indicated by an increased binocular acuity score of 7 or more letters with respect to the best monocular score on these charts, a threshold consistent with a meaningful visual change.[17-19]

Optical Coherence Tomography

Retinal structure was assessed through Spectral Domain Optical Coherence Tomography. The peripapillary RNFL and macular volume (both the average and quadrant distributions for each eye) were obtained through the application of the Spectralis OCT system (Software version 5.4; Heidelberg, Germany) and the peripapillary RNFL and macular volume (both the average and quadrant distributions for each eye) and average GCL-IPL thicknesses were obtained with a Zeiss-Cirrus High Definition-OCT 4000 system (Zeiss Meditec Dublin, CA, USA).

Critical Flicker Fusion

Critical flicker fusion rates were obtained through a device developed at the University of Iowa Department of Bioengineering, and are thought to represent the temporal conduction response characteristics of the visual circuit to a uniform flickering stimulus. Patients were tested by 'ramping up' the stimulus frequency from 20 to 40 Hz, and reporting to the investigator the point at which cessation of the flickering occurs and the stimulus is thereby perceived as a solitary static light. The stimulus frequency was then 'ramped down' from 40 to 20 Hz; with the patient reporting the point at which the static light is once again perceived as dynamically flickering light stimulus. The ramping up and down of the flickering light was performed a total of 6 times and the average frequency of perceived flicker was used to determine critical flicker fusion frequency.

Pulfrich Phenomenon

Patients were asked to indicate whether movement of a linearly moving pendulum ball followed a 2D versus a 3D elliptical object-motion trajectory (essentially in a Z direction in addition to an X and Y direction). In the case where object motion was not perceived to be limited to the frontal plane, subjects were asked to ascertain the magnitude and direction of the 3D motion, by virtue of the ball's approximation with respect to one of five coloured wires oriented horizontally in close vertical proximity to the ball, and placed equidistant to each other along the 'Z' plane (i.e. each wire was aligned horizontally with respect to the patient's view; albeit each was separated from each other along the patient's 'line of depth sight'; with wires both behind and in front of the wire representing the actual frontal ('X' or horizontal component of the object's motion) plane of the ball's motion [Figure 1].

The perception of the phenomenon of elliptical motion (i.e. the PF) was indicated by a categorical PF-score (0 representing the actual and horizontal/vertical axis of ball motion, while each successive wire in front of or behind the 0 plane was scored according to which wire the ball most closely approximated during its elliptical trajectory). This was reported by the patient, and designated an integer score from 0 to 4 representing the motion trajectory of the ball by the wire that was chosen. During each trial categorical ranking (0 to 4) was utilized by the subjects in order to 'score' the location of the ball's plane of apparent motion (whether in front of or behind the actual 'zero-z' plane) [Figure 1].

All patients had both eyes retested with a range of graduated neutral density filters (G-NDF), intended to artificially induce (in normal subjects), or to attenuate or abolish the experience of PF (in MS patients with a confirmed PF illusion) [Figure 4A and 4B]. Further, we also characterized MS patients with inter-eye asymmetry on other measures such as flicker fusion.

Statistical Analysis

For our statistical analysis we used the STATA 14.1 software (Stata Corp, College Station, TX) to analyze our data. We used a categorical linear regression model to compare the relationship between initial PF score and G-NDF required to abolish the PF [Figure 4A]. The Wilcoxon rank-sum test was applied to compare the PF scores between groups following G-NDF application [Figure 4B]. Control vs. MS and PF vs non-PF MS group status was examined as a predictor of continuous variables in the dataset using linear regression models, accounting for age. PF score was included in the regression models as an indicator variable of ordered categories. A two-sided Fisher's exact test was applied to compare the proportions of patients with binocular summation and the experience of the PF vs. those without PF. Statistical significance was considered for probability values less than 0.05.

RESULTS

Of the twenty-three patients with a history of AON, 12 subjects (52%) experienced PF whereas 11 subjects (48%) did not. None of our ten control subjects (n=0, 0%) experienced the PF spontaneously (i.e. without first artificially inducing this illusion with neutral density filters). Alternately, we were able to induce the PF in all control subjects, and in all MS patients that did not experience the PF spontaneously. Further, we found a corresponding increase in the illusory perceived depth of swing, indicated by a larger PF score, as we decreased object brightness by increasing the optical density of the neutral density filter. PF scores varied across MS patients who perceived the phenomenon, and there was a corresponding increase in the magnitude of neutral density filtering necessary to abolish the illusion of elliptical motion ($p<0.001$; Figure 4A).

We compared the MS group experiencing the PF with filtering over the unaffected fellow eye (PF MS FE; designated as the eye with no history of AON or in the case of bilateral AON the eye with greater RNFL thickness), MS group experiencing PF with filtering over the affected eye (PF MS AE; designated as the eye with history of AON or if bilateral AON the eye with lesser RNFL thickness), and control group (CTRL; only the right eye was filtered in this group) using the Wilcoxon rank sum test. There was a statistically significant decrease in PF score in the PF MS FE group upon filtering with the 0.6, 0.9, and 1.2 log filters ($p=0.042$, $p=0.04$, and $p=0.0238$, respectively) compared to the control group. There was no statistically significant difference between PF scores upon filtering the PF MS FE vs. filtering the PF MS AE, although the PF MS FE approached 0 while the PF MS AE tended to increase in PF score with greater filtering [Figure 4B].

In the non-PF group 7 out of 11 subjects (64%) were binocular summators while only 1 out of 12 in the PF group (8%) showed summation; this was statistically significant based on the two-sided Fisher's exact test (p=0.0062; Table 2) and was further confirmed with a logistic regression analysis accounting for age using summation status to predict PF vs. non-PF group classification (p=0.024). This observation suggests that visual system adaptation may have occurred in order to adjust the transmission properties across the two eyes, for the purpose of synchronizing the arrival of information at the visual cortices, thereby facilitating those processes involved in binocular fusion and stereopsis (depth perception).

Using a linear regression model accounting for age we found that the MS vs. control subtypes were significant predictors of RNFL thickness (p<0.001), GCL+IPL thickness (p<0.001), CFF (p=0.005), and low contrast visual acuity scores (p=0.009). There were no statistically significant differences between the PF and non-PF MS groups in inter-eye asymmetry measures of RNFL (p=0.451), GCL+IPL (p=0.298) or CFF (p=0.861), between the PF and non-PF MS groups though there was a trend of greater symmetry in the non-PF group [Table 2].

DISCUSSION

Recent work suggests that an inherent adaptive capability exists within the CNS to reduce the disparity of the transmission of object information emanating from the retinas, and ultimately converging upon the higher visual networks. This translation of the static and dynamic elements of our visual world allows for our visual perception of our environment.

In our study we describe our method for identifying the presence and magnitude of both the spontaneous PF (i.e. secondary to disease pathology), and the inducible PF achieved through the monocular application of graduated neutral density filtering (G-NDF) during the linear swinging ball paradigm. With the employment of this technique we can both produce as well as measure the magnitude of the PF in control subjects, while correspondingly facilitating the measurement of this phenomenon in MS patients.[6,13-15] Presence of stereoscopic vision, a pre-exquisite for perception of PF has carefully been demonstrated.

We hypothesized that the presence of two groups within the MS population (those that experienced PF spontaneously and those that did not) is the result of a failure in an adaptive mechanism within the visual processing network that would otherwise prevent the PF by somehow compensating for the inter-ocular asymmetry secondary to demyelination within the visual system[7,8].

The described changes in the visual evoked potential (VEP) by the longitudinal AON study performed by Raz et al.[7] indicate a temporal change in the transduction of visual information in both the affected and fellow eyes of unilateral AON subjects over time. Specifically there was slowing of the VEP latency in the FE's to match that of the AE's. This change in VEP latency was thought to be an adaptive phenomenon governed by cortical reorganization rather than the occurrence of demyelination in the FE. Thus, there could be delayed latencies in the FE's as the result of adaptation at the cortical level to improve binocular integration. Presumably, such integration of the VEP latencies between the two eyes would lessen the PF. This of course will only apply within a narrow range of inter-ocular VEP differences as PF cannot be observed if visual function in one eye is so poor, that visual information derived from it is suppressed.

Carl Pulfrich himself, who had gave credit to his colleague Fertsch for having discovered the phenomenon was unable to see the 3D elliptoid movement because he was blind in one eye [[1]]. Having such been sensitive to such a limitation he was nevertheless surprised by his binocular compatriots ignorance of the phenomenon [2]. He remarks that the swinging pendulum can be seen in every clock case in every household and no one seems to perceive that the swing my not be in the 2D plane [[2]]. The detailed experiments Pulfrich had designed were however motivated by a more mundane motive. He had developed stereoscopy for his company Zeiss for commercial and military purposes. Stereoscopy enabled rapid and precise mapping of cards, rendering time consuming triangulation unnecessary. Likewise stereoscopy could be used to help increase ballistics for the military. In essence technique just made use of what evolution had discovered in the Cumbrian epoch [[3]]. There was however one essential potential flaw to the technique which had been published by the at the time world famous astronomer Max Wolf [4] . Some objects could not be measured with certainty in a 2D plane [[1]]. It was to Pulfrichs credit that he could demonstrate that presentation of an object to either eye with unequal illumination was the reason for the illusory movement in a 3D space [[2]]. Since, the film industry has caught up and makes use of the PF for production of 3D movies requiring glasses which are tinted unequal between the eyes. Neuro-ophthalmologists have noted the diagnostic potential of the test [5] . The time of the pendulum wall clock is gone and as our world has accelerated, patients nowadays are aware of the PF and notice the impact on their daily living activities and quality of live [McGowan G, et al. present reference 2].

Our investigation demonstrates visual illusions, as the result of asymmetric processing of visual information to the visual cortices, may result in dangerous perceptual distortions. Such illusions of depth perception may impair driving, operating machinery or performing tasks that require 3D perception of our visual environment. The accuracy of perceiving our 3D stereoscopic space relies upon our ability to reconcile the correct aspects of an object, its location and its spatial-temporal relationships to other targets.

These potentially serious miscalculations in object location, trajectory, and velocity and acceleration can result in critical errors in visual judgment. For instance, in an MS patient with a left eye optic neuritis, there may be confusion about the location of a car driving in an adjacent lane of traffic [Figure 3]. PF is the illusion that an object moving linearly along a 2-D plane is instead perceived as exhibiting an elliptical 3-D trajectory, moving across the ‘x’, ‘y’, and ‘z’ planes [Figure 1]. This phenomenon is hypothesized to reflect an inter-eye discrepancy in the timing of the delivery of visual information, or a delay in the perceptual processing mechanisms necessary for object identification in the visual cortex. This phenomenon most commonly occurs secondary to asymmetric damage to the visual system (e.g. acute optic neuritis; AON).[1-6] Further the PF also likely reflects a degree of interpatient heterogeneity in that a proportion of patients fail to engage centrally adaptive mechanisms capable of neutralizing the inter-eye timing discrepancy within the visual processing circuitry.[7,8] Binocular summation (BS), as seen in our study, may be a factor that lessens the risk for the PF to occur.

In future studies we hope to further distinguish the PF and non-PF MS groups with the hopes of better characterizing the possible adaptive mechanisms involved in the experience of the PF through measures of functional and structural integrity (e.g. multifocal visual evoked potential and spectral domain optical coherence tomography).

The ability to objectively identify the presence and magnitude of the PF can be used for the investigation of changes in visual system networks and their corresponding functional consequences. The application of G-NDF to the FE of MS patients experiencing PF can be utilized to identify the magnitude of filtering necessary to abolish the effect in these subjects, and the incorporation of a corresponding filter into either contact lenses or spectacles can serve as a simple yet practical intervention with important ramifications for the patient's safety and quality of life.

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Figure Legends

Figure 1: ***The PF in Normal Subjects (via G-NDF) and MS patients.*** The top left diagram shows how a subject with structurally and physiologically symmetrical eyes would perceive a moving object (the solid red ball) following an arc along a linear trajectory (A). The application of a NDF (black bar; B1) over the left eye of the control subject produces the PF; with the bob of the pendulum appearing (hatched red ball) to be further away (in an elliptical trajectory) when its direction of motion is away from the filtered eye (B1); whereas movement of the bob toward the filtered eye appears closer to the observer (i.e. the front aspect of the ellipse; B2). Row C, illustrates the illusory visual experience of the PF in MS patients with inter-eye asymmetry with respect to visual system pathology. In C1, we depict the illusion of the pendulum bob appearing to move in a trajectory further away (hatched red ball) from the actual object motion (solid red ball), when the bob's actual motion is away from the more affected eye (eye with a red X). Correspondingly, in C2, the bob is moving in a direction toward the more abnormal eye, and thereby is perceived by the patient to be closer (hatched red ball) in appearance (i.e. at the front of the ellipse) than the actual linear motion of the bob (solid red ball). Finally, in D, a NDF magnitude can be identified and applied to the more *normal* eye of the MS patient, in order to attenuate or abolish the PF (theoretically by reducing object brightness and thereby delaying the transmission of visual information to the visual cortex; commensurate with that being transmitted by the abnormal eye; and thereby achieving timing arrival synchronization.

Figure 2: Here we show an illustration that depicts a previous AON in the left eye, and the corresponding delay in the transmission of visual information emanating from this eye. However, in the lower portion of the illustration, we are instructed on the application of the graduated neutral density filter to the fellow, less affected eye. We can adjust the filter such that we can reduce the propagation of visual information originating from the right eye. This intervention is highly effective in promoting the synchronized arrival of visual information at the level of the visual cortices.

Figure 3: Here we detail a real life example of how Pulfrich's phenomenon can impair the safety of driving. At the top of the illustration, in Scenario A1 we have an MS patient driving in the green car, who has sustained an episode of left acute optic neuritis. As the red car transitions from left to right in front of the green car, the vector of the red car is actually moving away from the left eye affected by optic neuritis. In such a case, the red car is perceived (a true visual illusion) as being actually further forward than it actually is. Such a circumstance could easily precipitate a rear end accident. Lower on the illustration in Scenario A2, the red car now alternately is driving to the right of the green car, which eventually changes lanes, ultimately ending up in front of the green car containing our MS patient with a history of severe left optic neuritis. In this scenario the vector of the red car's movement is toward the affected left eye, leading to the perceptual illusion in our patient, who now believes that the red car is much closer to the front of his car; hence he reduces his speed and increases the distance behind the red car. Finally, in Scenario B, the patient has had the discrepant delivery of visual object information to the visual cortices mitigated, if not completely synchronized by the application of a neutral

density filter (NDF) to the right, less affected eye, and adjustments in the level of tint that ultimately leads to neutralization of the Pulfrich effect, with the moving bob now traversing only the horizontal ('x') and vertical ('y') planes.

Figure 4: In **4A** we illustrate the relationship and correlation between increased PF score and degree of tinting required to eliminate or attenuate the visual illusion of elliptical 3D motion. The corresponding G-NDF to abolish the PF was best predicted for those with a PF score of 1. In **4B** we demonstrate the relationship between the gradual escalation in the tint covering either the affected eye (i.e. with a history of AON in an MS patient) or unaffected eye with the neutral density filter (G-NDF). Further we show that the application of tinting to an eye from a normal subject can also produce the Pulfrich phenomenon, with a significantly correlated relationship between the intensity of filtering and the PF score. The affected eye (AE) is determined as having a history of AON or lower RNFL thickness in case of bilateral AON. The fellow eye (FE) has no history of AON or greater RNFL thickness in the case of bilateral AON. (* = $p<0.05$; CTRL OD = average PF scores of control group with filtering over the right eye, Non-PF AE = filtering placed over affected eye of MS group that did not experience PF, Non-PF MS FE = filtering placed over the fellow eye of MS group that did not experience PF, PF MS FE = filtering placed over the fellow eye of MS group that did experience PF, and PF MS AE = filtering placed over the affected eye of the MS group that did experience the PF)

Table 1: Normal Subjects and MS Patient Characteristics

	CTRL	**MS**	**p**
N (%)	10 (30.3)	23 (69.7)	
Age (SD)	27.6 (7.35)	40.7 (11.4)	0.003*
PF (%)	0 (0)	12 (52.2)	<0.001*
LCLA (SD)	33.4 (6.78)	24.8 (9.33)	0.009*
RNFL (SD)	101.35 (10.3)	83.6 (13.3)	<0.001*
GCL+IPL (SD)	84.4 (5.22)	70.9 (9.76)	<0.001*
CFF (SD)	33.4 (2.03)	29.3 (3.91)	0.005*

Table 2: Relationship between MS Patients with NON-PF and PF Scores and Low Contrast Vision, Retinal Thickness, and Critical Flicker Fusion

	Non-PF	**PF**	**p**
N (%)	11 (47.8)	12 (52.2)	
BS at LCLA (%)	7 (63.6)	1 (8.33)	0.0062*
RNFL IE Difference (SD)	11 (7.33)	15.9 (13.5)	0.451
GCL+IPL IE Difference (SD)	9.09 (6.74)	13.8 (10.3)	0.298
CFF IE Difference (SD)	3.32 (3.40)	3.44 (3.30)	0.861

Author Contributions

Millad Sobhanian made substantial contributions to the conception or design of the work, acquisition, analysis, and interpretation of the data. He further contributed to the drafting of the work and its critical revision important for intellectual content, and approved the final version of the manuscript to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Rohit Agarwal made substantial contributions to the conception or design of the work, acquisition, analysis, and interpretation of the data. He further contributed to the drafting of the work and its critical revision important for intellectual content, and approved the final version of the manuscript to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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