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RESEARCH

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Optical coherence tomography findings in children of patients with Alzheimer-type dementia

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Abstract

Background Ocular imaging receives much attention as a source of potential biomarkers for dementia. This study aims to study structural changes in the retina and optic nerve in children of healthy and demented parents and to confirm the applicability of optic nerve tomography as a potential noninvasive marker for the early diagnosis of dementia.

Methods Healthy individuals with a parent diagnosed with Alzheimer's disease (AD) and healthy controls with healthy parents were included in the study. Included individuals had undergone Montreal Cognitive Assessment Scale and Mini-Mental Test by a single neurologist physician to confirm not having dementia. All the subjects then underwent a complete ophthalmological examination, including refractive error and keratometry readings, best-corrected visual acuity measurement with a Snellen chart (converted to LogMAR), intraocular pressure (IOP) measurement, slit-lamp biomicroscopy, dilated fundus examination, axial length measurement and optical coherence tomography (OCT) for the parapapillary retinal nerve fiber layer (pRNFL), basal membrane opening—minimum rim width (BMO-MRW), and macular thickness analysis. Only the right eyes of the subjects were evaluated. OCT findings of these two groups were compared.

Results The temporosuperior sector the pRNFL thicknesses at all 3 circles (3.5, 4.1, and 4.5) were significantly thinner in the children of the dementia group than in healthy controls ($p = 0.023$, 0.039, and 0.016, respectively). For the remaining sectors, the thicknesses of the pRNFL were also thinner, however, the differences were not significant ($p > 0.05$ for all). BMO-MRW at all sectors, were not also different significantly between the groups ($p > 0.05$ for all). Parents' dementia grade were found to be an important factor that the BMO-MRW at the temporal sector, got thinner with increasing grade ($B = -20.631$, 95% CI − 42.121 to − 0.019, and $p = 0.049$).

Conclusion We believe that OCT can be used as a noninvasive biomarker in the preclinical period, when supported by more extensive studies in people whose parents have AD.

Keywords Optical coherence tomography, Parapapillary retinal nerve fiber layer, Dementia patient's children, Early diagnosis of Alzheimer's disease, Basal membrane opening—minimum rim width, Optic nerve

Introduction

Cognitive impairment is major medical, social, and economic public health issue worldwide with significant implications for life quality in adults. The population continues to age and the prevalence of Alzheimer disease (AD) is expected to grow. At present, there is no curative treatment for AD. A definitive diagnosis of AD

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can only be made through histopathologic examination. Recent investigations have explored whether the structural changes of the retina and optic nerve can provide screening for early detection of AD [1, 2]. Economic, social problems caused by AD reveal the importance of early diagnosis and treatment of the disease. Ophthalmologic impairments have also been reported in AD. These symptoms of visual dysfunction in AD have been associated with the degeneration of anterior visual pathways. There are many research articles in the literature on these two topics [3, 4]. Based on these articles, we compared the pRNFL and BMO-MRW in the children of individuals with dementia with a control group of similar age and gender. Recognition of the disease in the pre-symptomatic period will contribute to the study of etiopathogenesis and neuroprotective therapy. The data obtained from these studies will be used to solve economic, social and individual problems caused by AD. This study aims to study structural changes in the retina and optic nerve in children of healthy and demented parents and to confirm the applicability of optical nerve tomography as a potential noninvasive marker for the early diagnosis of AD. We think that OCT has a promising role in this phase.

Methods

Subjects and methods

The study was a cross-sectional prospective study approved by Hitit University School of Medicine Ethics Committee (349/2021) and conducted by STROBE guidelines for reporting observational studies (www.strobestatement.org) and the Declaration of Helsinki. All participants gave their informed consent for this study. Individuals between the ages of 25 and 65 with a diagnosis of mild or moderate AD in one of their parents were included in the study. On the other hand, individuals of similar age and gender whose parents were cognitively healthy were selected for the control group. Excluded from the study were the individuals diagnosed with dementia based on clinical anamnesis and examination findings, patients with ocular pathologies (cataract, glaucoma, corneal diseases, such as dry eye and > 3D astigmatism, retinal diseases, uveitis, or ocular surgery history), those with systemic diseases that could cause changes to the ocular and neurological physiology (diabetes mellitus, connective tissue diseases, and autoimmune diseases), and those with OCT artifacts and anatomic variations such as insufficient OCT quality (quality score < 20), segmentation errors, vitreoretinal interface problems, optic disc drusen, and chorioretinal scarring. Healthy individuals with a parent (mother and/or father) diagnosed with AD according to the criteria of the National Neurological and Communication Diseases and Stroke Institute/Alzheimer's Disease and Related Disorders Association and healthy controls with healthy parents included in the study. Included subjects were undergone Montreal Cognitive Assessment Scale and Mini-Mental Test by a single neurologist physician to confirm not having dementia. All participants also underwent a complete ophthalmological examination, including refractive error and keratometry readings (Tonoref III, Nidek Co. Ltd, Aichi, Japan), best-corrected visual acuity assessed using a Snellen chart (converted to LogMAR), intraocular pressure (IOP) measurement, slit-lamp biomicroscopy, dilated fundus examination, axial length measurement (AL-SCAN, Nidek Co. Ltd, Aichi, Japan), and OCT (Spectralis OCT Heidelberg Engineering, Heidelberg, Germany) for pRNFL thickness, BMO-MRW, and macular thickness analysis. The parents of the volunteers in both groups participating in the study underwent a complete eye examination. Only the right eyes of the subjects were evaluated. OCT findings of these two groups were compared.

Analyses of the OCT measurements

Spectralis OCT was used for the measurement of the BMO-MRW and pRNFL thicknesses. This device has a scan rate of 40,000/s using a light source of 820 nm. For both pRNFL and the BMO-MRW thickness measurements, glaucoma module premium edition software was used. For each eye with non-dilated pupil, automated anatomically positioning system detects the fovea center and Bruch's membrane opening center, thereby preventing incorrect measurements due to the torsion of the eyes. After detection of the foveal center, two scan patterns were obtained: optic nerve head (24 radial scans centered on BMO) and peripapillary scans (3 concentric circle scans of 3.5, 4.1, and 4.5 mm in diameter). BMO-MRW was defined as the shortest distance between the BMO and the internal limiting membrane. For the pRNFL evaluation, a 12° circular scan was used to measure pRNFL thickness. Global and six sectors of (superotemporal, temporal, inferotemporal, inferonasal, nasal, superonasal) RNFL thicknesses from the 3 circles and BMO-MRW parameters were measured automatically by the device.

Statistical analysis

The sample size of the study was calculated using G*Power software (ver. 3.1.9.4 Dusseldorf, Germany) (for the difference between two different means; effect size d: 0.60; medium to large effect, α error: 0.05, power: 0.95, allocation ratio: 1, total sample size: 146). Jamovi ver. 1.6 (computer software, https://www.jamovi.org) was used for statistical analysis. Quantitative variables were defined as mean and standard deviation (sd) and qualitative variables as percentages. The Shapiro–Wilk test was

used to evaluate whether the sample came from a normally distributed population. According to the results of the normality analysis, the pRNFL and BMO-MRW were compared between the groups using the parametric Student's *t*-test or non-parametric Mann–Whitney U test. The distribution of the nominal and ordinal factors, such as gender was compared between the groups using Pearson's Chi-squared test. After the collinearity diagnostics, a linear regression model was created for each pRNFL of the 4.1 mm diameter circle and BMO-MRW sector to explore the associations of the pRNFL and BMO-MRW thickness with age, OCT quality score, and BMO area as coefficients, and gender and group as factors. The dementia grade of the parents was also used as a factor only for the children of the dementia population. Results of the regression models were given with regression coefficient (R^2), estimate (B), confidence interval (CI), and p values. A p value less than 0.05 considered statistically significant.

Results

Demographic data and clinical findings

A total of 81 subjects with a parent with dementia (Group 1) and 76 healthy volunteers (Group 2) were included in this study. There was no missing data of the study subjects. There were remaining 76 eyes in group 1 and 74 eyes in group 2. The groups showed similar distribution concerning age and gender (p = 0.471, and 0.404, respectively). The average age of the group with Alzheimer's parents was found to be 45.93 + 10.21. 53.9% of the participants were women and 46.1% were men. In this group, 30 of the parents had mild and 46 had moderate AD. In the control group, the average age was found to be 44.91 + 8.79, while 54.1% of the participants were female and 45.9% were male.

There was no significant difference between the groups in terms of the IOP, BMO area, and quality of the OCT scanning (p = 0.239, 0.255, and 0.199, respectively). The demographic data are shown in Table 1.

Results of the spectral domain OCT scanning

The mean values with sd of the pRNFL and BMO-MRW thicknesses for all sectors and the results of the comparisons between the groups are presented in Tables 2 and 3, respectively. Only for the temporosuperior sector the pRNFL thicknesses at all 3 circles (3.5, 4.1, and 4.5) were significantly thinner in the children of the dementia group than in healthy controls (p = 0.023, 0.039, and 0.016, respectively). For the remaining sectors, the thicknesses of the pRNFL were also thinner; however, the differences were not significant (p > 0.05 for all). BMO-MRW at all sectors, were not also differ significantly between the groups (p > 0.05 for all). However, the healthy controls had slightly thicker BMO-MRWs than the children of dementia parents. The results of the linear regression models for pRNFL thickness and BMO-MRW sectors are given in Tables 4 and 5, respectively. Regression analysis revealed that the pRNFL thickness and BMO-MRW were all associated with the BMO area (the true anatomical optic disc size) except for the inferonasal and the nasal sectors of the pRNFL (p = 0.201 and 0.194 for inferonasal and nasal sectors, respectively, and < 0.05 for the remaining). At the temporosuperior sector pRNFL thickness found to be thinner in the children of dementia independent from age, gender, BMO area, and the quality of the OCT scanning (B = − 5.690, 95% CI − 12.349 to − 0.871, and p = 0.039). Parents' dementia grade were found to be an important factor that the BMO-MRW at the temporal sector, got thinner with increasing grade (B = − 20.631, 95% CI − 42.121 to − 0.019, and p = 0.049). The OCT quality score was found not to be associated with both pRNFL thickness and BMO-MRW at any sector.

Discussion

AD is the most common neurological disorder worldwide, and it is estimated that 1 in 3 of those born in developed countries today will develop dementia during their life [5]. AD is a progressive neurodegenerative disorder

Table 1 Demographic data and the clinical findings of the study participants

	Children of dementia (n=76)		Healthy controls (n=74)	P
Age (years, sd)	45.93 + 10.21		44.91 + 8.79	0.471
Female (n,%)	41 (53.9%)		40 (54.1%)	
Male (n,%)	35 (%46,1)		34 (% 45,9)	0.404
Grade of dementia (n,%)	**Mild**	**Moderate**	n/a	n/a
	30 (39.4%)	46 (60.6%)		
IOP (mmHg, SD)	14.21 + 3.22		14.68 + 3.14	0.239
BMO area	2.06 + 0.40		2.00 + 0.41	0.255
OCT quality score	21.32 + 5.71		23.88 + 6.01	0.199

sd standard deviation, *IOP* intraocular pressure, *BMO* basal membrane opening, *OCT* optical coherence tomography

Table 2 The mean pRNFL thicknesses of the sectors

	Children of dementia (n = 76)	Healthy controls (n = 74)	P
RNFLgl			
3.5	103.41 + 10.43	106.68 + 11.36	0.091
4.1	88.04 + 9.50	90.20 + 8.97	0.256
4.5	76.89 + 7.44	78.05 + 8.01	0.506
RNFLts			
3.5	129.68 + 20.97	133.71 + 21.83	0.023
4.1	117.25 + 17.98	121.41 + 14.04	0.039
4.5	106.65 + 15.98	110.93 + 12.08	0.016
RNFLns			
3.5	122.65 + 26.07	129.29 + 27.17	0.103
4.1	99.40 + 20.14	102.60 + 21.04	0.233
4.5	82.75 + 18.64	83.21 + 16.75	0.762
RNFLti			
3.5	150.11 + 21.66	154.15 + 18.63	0.301
4.1	134.60 + 20.98	136.62 + 15.05	0.962
4.5	121.71 + 18.64	122.84 + 16.75	0.481
RNFLni			
3.5	122.91 + 24.97	125.40 + 20.07	0.295
4.1	97.15 + 20.81	99.90 + 16.68	0.275
4.5	78.88 + 17.69	80.27 + 12.75	0.291
RNFLt			
3.5	72.67 + 11.56	74.51 + 10.06	0.162
4.1	64.69 + 10.42	66.00 + 9.09	0.293
4.5	58.14 + 8.80	59.45 + 7.30	0.265
RNFLn			
3.5	88.87 + 14.71	89.20 + 12.72	0.714
4.1	72.97 + 12.02	73.93 + 10.12	0.988
4.5	62.50 + 9.57	61.93 + 9.27	0.654

pRNFL parapapillary retinal nerve fiber layer, *gl* global, *ts* temporal superior, *ns* nasal superior, *ti* temporal inferior, *ni* nasal inferior, *t* temporal, *n* nasal, *RNFL* retinal nerve fiber layer

Table 3 The mean BMO-MRW of the sectors

	Children of dementia (n = 76)	Healthy controls (n = 74)	P
BMO-MRWgl	343.87 + 52.78	344.61 + 52.16	0.836
BMO-MRWts	321.19 + 67.48	326.09 + 58.32	0.833
BMO-MRWns	377.81 + 76.21	382.19 + 60.89	0.483
BMO-MRWti	362.76 + 66.09	364.88 + 63.01	0.376
BMO-MRWni	406.44 + 72.91	417.63 + 65.73	0.501
BMO-MRWt	252.70 + 53.48	259.71 + 49.89	0.405
BMO-MRWn	377.03 + 67.22	385.38 + 72.46	0.247

BMO-MRW basal membrane opening—minimum rim width, *gl* global, *ts* temporal superior, *ns* nasal superior, *ti* temporal inferior, *ni* nasal inferior, *t* temporal, *n* nasal

Table 4 Results of the regression models which searched for the associations with the pRNFL thickness

	B	CI	P
RNFLgl R2 = 0.138			
Group	− 1.909	− 4.831/0.514	0.099
Grade of dementia	0.153	− 3.748/4.051	0.938
BMO area	7.690	4.354/11.028	< 0.001
OCT quality score	− 0.156	− 0.501/0.187	0.369
RNFLts R2 = 0.090			
Group	− 5.690	− 12.349/− 0.871	0.039
Grade of dementia	− 0.765	− 8.535/7.005	0.845
BMO area	9.614	3.401/15.829	< 0.001
OCT quality score	− 0.147	− 0.788/0.444	0.651
RNFLns R2 = 0.091			
Group	− 4.728	− 11.352/0.059	0.071
Grade of dementia	0.829	− 7.776/9.434	0.849
BMO area	10.652	3.091/18.219	0.006
OCT quality score	− 0.431	− 1.210/0.329	0.277
RNFLti R2 = 0.041			
Group	− 0.584	− 6.761/5.598	0.852
Grade of dementia	− 1.962	− 10.653/6.740	0.655
BMO area	8.160	1.110/15.211	0.024
OCT quality score	− 0.415	− 1.142/0.312	0.261
RNFLni R2 = 0.019			
Group	− 2.834	− 9.855/3.583	0.385
Grade of dementia	− 6.785	− 10.934/5.520	0.125
BMO area	4.758	− 2.570/12.088	0.201
OCT quality score	− 0.023	− 0.770/0.732	0.951
RNFLt R2 = 0.113			
Group	0.188	− 2.969/3.346	0.906
Grade of dementia	− 0.955	− 5.281/3.337	0.662
BMO area	6.259	2.655/9.864	< 0.001
OCT quality score	− 0.067	− 0.439/0.304	0.720
RNFLn R2 = 0.121			
Group	− 1.156	− 4.781/2.469	0.530
Grade of dementia	− 1.159	− 5.582/3.534	0.625
BMO area	3.711	− 1.503/12.088	0.194
OCT quality score	− 0.456	− 2.742/1.442	0.376

RNFL retinal nerve fiber layer, *OCT* optical coherence tomography, *BMO* basal membrane opening

characterized by impairment of cognition and behavior, with significant physical, psychological, social, and economic implications. The main hallmark of AD is the accumulation of extracellular amyloid-beta (Aβ) plaques and intracellular tau neurofibrillary tangles comprising

Table 5 Results of the regression models which searched for the associations with the BMO-MRW

	B	CI	P
BMO-MRWgl R2 = 0.113			
Group	− 2.700	− 20.160/14.361	0.760
Grade of dementia	− 12.111	− 34.607/10.375	0.288
BMO area	− 42.719	− 62.688/− 22.821	< 0.001
OCT quality score	− 1.097	− 3.151/0.958	0.293
BMO-MRWts R2 = 0.086			
Group	− 2.256	− 22.366/− 17.855	0.826
Grade of dementia	− 14.309	− 41.307/0.903	0.093
BMO area	− 41.616	− 64.019/− 18.101	< 0.001
OCT quality score	− 0.900	− 3.771/1.467	0.454
BMO-MRWns R2 = 0.115			
Group	− 10.498	− 33.170/2.171	0.098
Grade of dementia	− 6.911	− 40.101/17.804	0.658
BMO area	− 51.517	− 77.398/− 25.640	< 0.001
OCT quality score	− 1.653	− 4.331/1.102	0.223
BMO-MRWti R2 = 0.095			
Group	− 4.320	− 16.192/11.827	0.578
Grade of dementia	− 6.683	− 31.970/18.624	0.602
BMO area	− 36.311	− 59.714/− 12.899	0.003
OCT quality score	− 1.053	− 3.321/1.009	0.343
BMO-MRWni R2 = 0.150			
Group	− 8.412	− 30.819/13.391	0.447
Grade of dementia	− 5.277	− 33.887/23.324	0.715
BMO area	− 61.881	− 86.770/− 36.995	< 0.001
OCT quality score	− 1.241	− 5.426/0.912	0.425
BMO-MRWt R2 = 0.021			
Group	− 2.651	− 19.486/14.180	0.756
Grade of dementia	− 20.631	− 42.121/− 0.019	0.049
BMO area	− 15.542	− 34.765/− 3.675	0.002
OCT quality score	− 0.552	− 2.385/1.099	0.644
BMO-MRWn R2 = 0.120			
Group	− 14.208	− 36.297/7.883	0.206
Grade of dementia	− 9.0.78	− 37.661/19.500	0.530
BMO area	− 56.412	− 81.321/− 31.623	< 0.001
OCT quality score	− 0.6124	− 3.511/0.993	0.518

BMO-MRW basal membrane opening—minimum rim width, *gl* global, *ts* temporal superior, *ns* nasal superior, *ti* temporal inferior, *ni* nasal inferior, *t* temporal, *n* nasal, *OCT* optical coherence tomography, *BMO* basal membrane opening

phosphorylated tau protein resulting in profound brain atrophy. Previous studies have indicated that vascular risk factors affecting the cerebral microcirculation may also contribute to AD pathogenesis, and microvascular pathologies are present in the majority of AD patients [6]. The diagnosis of AD is primarily clinical and relies on neuropsychological evaluation, as biomarker detection relies on examination of cerebrospinal fluid (CSF) and positron emission tomography (PET) scan, costly and invasive procedures that pose risks to patients [7]. At present, there is no curative treatment for AD. As most of the trials so far have focused on patients already suffering from AD, it is postulated that more success may be achieved by targeting those who still are cognitively intact [8, 9]. This poses a new problem. How can we recognize those at risk for the development of AD when there are no clinical symptoms yet? PET scanning has provided a breakthrough in diagnosing these cases of preclinical AD. The process of Aβ accumulation in the brain is a gradual one, which often has been ongoing for decades before the onset of clinical symptoms [10]. By using tracers sensitive to Aβ, PET enables visualization of Aβ presence in vivo in cognitively healthy individuals. The presence of Aβ deposits in the brain of healthy individual is a risk for developing AD [11, 12]. However, as reliable as this technique may be, it is currently not suitable for large-scale screening. It is a costly diagnostic procedure that is only available in larger hospitals [13]. This illustrates the urgent need for an easy, noninvasive and reliable biomarker for preclinical AD. The eye, and more specifically the retina, shares many similarities with the brain. Both are derived from the same embryological tissue and consist of a complex combination of neuronal tissue and glial cells. One could consider the retina to be an extension of the brain [14, 15]. Many studies have already illustrated changes in the retina of individuals suffering from AD, such as retinal thinning and vascular changes [16, 17]. A study in return close follow-up OCT and OCT angiography show great potential as noninvasive technologies for the diagnosis of AD. However, further research is needed to determine whether there are AD specific patterns of structural or microvascular change in the retina and optic nerve that distinguish AD from other neurodegenerative diseases. Development of sensitive and specific OCT/OCT angiography parameters will be necessary before they can be used to detect AD in clinical settings [18]. OCT, OCT angiography, fundus photography, and dynamic vessel analyzer are new imaging methods providing a quantitative assessment of retinal structural and vascular indicators such as thickness of the inner retinal layers, retinal vessel density, foveal avascular zone area, tortuosity and fractal dimension of retinal vessels, and microvascular dysfunction-for cognitive impairment and dementia. Should further studies need to be conducted, these retinal alterations may prove to be useful biomarkers for screening and monitoring dementia progression or early diagnosing in clinical routine [19]. Results of the

literature provide evidence of the potential use of OCT-measured parafoveal granular cell layer-inner plexiform layer (GCIPL) thickness to monitor neurodegeneration and to predict the risk of cognitive worsening over time [20]. Many people with dementia-diagnosed parents always have the same question in mind. Am I going to have dementia too? Our answers to this question especially for children who take care of parents with dementia, are very limited. Our aim in the study was to seek an answer to this question. As a matter of fact, we obtained statistically positive results.

A retrospective study showed that GCIPL thickness best correlated with memory, global cognitive performance, clinical dementia rating, and hippocampal atrophy [21]. Many studies have detected changes in different layers of the retina in patients with mild cognitive impairment [22, 23]. Thinning of the GCIPL has also been associated with cognitive deterioration in Parkinson's patients [20]. In another population-based study, Girbardt et al. report that thinner RNFL thickness was found to be a meaningful index for poorer cognitive performance which presents the potential for prediction of future cognitive decline [24]. In our study, retinal and optic nerve structures of cognitively normal individuals but whose parents have dementia were evaluated and significant statistical results were obtained. In our study, our goal was to detect abnormal findings in the OCT of people whose parent's had Alzheimer's dementia. In the group whose parents had AD, we found at the temporosuperior sector pRNFL thickness found to be thinner in the children of dementia parents independent from age, gender, BMO area, and the quality of the OCT scanning. Parents' dementia grades were found to be an important factor that the BMO-MRW at the temporal sector, got thinner with increasing grade. One of the limitations of our study, in which we took only one volunteer individual from each family, was that we did not extract detailed genetic genealogies of the families. Genetic tests for AD in our country, or the evaluation of markers in cerebrospinal fluid, are expensive and limited. This is an important reason for the restriction in our work.

Conclusion

We believe that OCT can be used as a noninvasive biomarker in the preclinical period, when supported by more extensive studies in people whose parents have AD.

List of Abbreviations

AD	Alzheimer's disease
OCT	Optical coherence tomography
pRNFL	Parapapillary retinal nerve fiber layer
BMO-MRW:	Basal membrane opening minimum rim width
IOP	Intraocular pressure
sd	Standard deviation
Aβ	Amyloid-beta
CSF	Cerebrospinal fluid
PET	Positron emission tomography
GCIPL	Granular cell layer-inner plexiform layer

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Author contributions
SE analyzed and interpreted the patient data regarding the collecting data, applying statistical tests, analyzing data. SA helped to collect patient data. Collecting data. HY was a contributor in analyzing data.

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Availability of data and materials
The authors confirm that the data supporting the findings of this study are available within the article [and/or] its additional materials.

Declarations

Ethical approval and consent to participate
This study was approved by the Hitit University School of Medicine Ethics Committee (349/06.01.2021) and conducted by following STROBE guidelines for reporting observational studies. The study was approved by the institutional ethics review board and complied with the Declaration of Helsinki. All participants gave their informed consent for this study.

Consent for publication
All authors gave their informed consent for publication of the article. Detailed consent was obtained from each individual participating in the study.

Competing interests
All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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