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RESEARCH ARTICLE

Memory-driven eye movements prospectively predict dementia in people at risk of Alzheimer's disease

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Abstract

Introduction: Oculomotor behaviors linked to cognitive performance revealed neurocognitive features of Alzheimer's disease (AD) that can enhance the accuracy of its assessment and diagnosis.

Methods: A sample of 107 participants (i.e., 65 mild cognitive impairment [MCI] and 42 controls) were recruited and followed up for 40 months. At baseline, they underwent assessment with the ViewMind digital biomarker, which draws cognitive-related patterns of eye movement while people perform the visual short-term memory binding task.

Results: Baseline data predicted that 36 patients with MCI would progress to the AD clinical syndrome (ADS Progressing). The remaining 29 MCI patients were predicted to remain as MCI or progress to other forms of dementia. After 40 months of follow-up, 94% of ADS Progressing patients had received a diagnosis of dementia, whereas none of the non-ADS Progressing had.

Discussion: The analysis of eye movement behavior combined with cognitive markers for AD can effectively predict progression to ADS among patients with MCI.

KEYWORDS
Conversion to Alzheimer's disease syndrome, digital biomarker, follow-up study, mild cognitive impairment

1 | INTRODUCTION

The diagnosis of Alzheimer's disease (AD) relies on a thorough clinical workup, which combines cognitive, imaging, and biological tests.[1,2,3] Such procedures currently carry only a modest predictive value in patients with mild cognitive impairment (MCI).[4] Differentiating cognitive decline due to aging from MCI at an early stage of AD has proved particularly challenging.[5] Cognitive screening tests are frequently informative at an advanced stage of the disease and are subject to mental status changes over time.[6,7] Neuropsychological tests have shown varying levels of accuracy and can be impacted by the individual's sociocultural background.[8,9] Advanced neuroimaging methods adhering to the new biomarker framework have good predictive value in the early stages of neurodegenerative diseases; however, their costs are prohibitive. We are lacking reliable and affordable diagnostic tools that can consistently predict AD dementia in patients at risk, such as those with MCI.[10]

Recent evidence suggests that the analysis of eye movements during visual exploration can inform on impaired cognitive processes. Meghanathan et al.[11] reported that viewing fixation duration is

sensitive not only to attention, but also to memory and processing load. We have observed recently that oculomotor behaviors linked to cognitive performance revealed neurocognitive features of AD that can enhance the accuracy of its assessment.[12] By combining the assessment of visual short-term memory binding (VSTMB), a cognitive function known to be a preclinical marker for AD,[13,14,15] and eye-tracking, we have demonstrated that both fixation behaviors and pupil responses can reliably discriminate between patients with suspected AD dementia and healthy older adults. The extent to which such a digital biomarker can predict the risk of dementia among older adults experiencing abnormal cognitive decline (i.e., MCI) remains unknown.

Considering the previously reported sensitivity of the VSTMB tests for AD, we investigated the hypothesis that such a cognitive marker combined with eye-tracking measures (i.e., a novel digital biomarker) would reliably identify patients with MCI who will progress to the AD clinical syndrome (ADS). If the previously reported specificity of such assessments in individuals at risk holds for this novel digital biomarker, we also predicted that it would discriminate between those patients with MCI who will progress to ADS and those who would develop other forms of dementia or would continue as MCI.

RESEARCH IN CONTEXT

1. **Systematic Review**: The literature was reviewed using PubMed. Current findings from eye movement analysis and cognitive processing to identify markers of conversion from mild cognitive impairment (MCI) to Alzheimer's disease (AD) are both scarce and inconclusive. Eye movements recorded during the visual short-term memory binding task (VSTMBT) have shown promise in cross-sectional analysis. Prospective prediction based on longitudinal data is needed. Given than MCI is a heterogeneous condition with uncertain prognosis, reliable and cost-effective assessment methods are needed to ascertain the potential trajectories that affected patients would follow.
2. **Interpretation**: Our data confirmed that the presence of abnormal eye movements (abnormal saccades and fixation durations) during the VSTMBT can prospectively predict the MCI patients who will progress to AD or other types of dementia. We demonstrated that predictions made using baseline data coherently matched clinical decisions made in successive follow-up assessments. Therefore, we propose that oculomotor responses linked to the VSTMBT are a preclinical digital biomarker for AD.
3. **Future Directions**: Further studies are necessary to validate the cognitive biomarkers proposed here against pipeline AD biomarkers.

2 | METHODS

The study was carried out at AXIS Neurociencias (Bahía Blanca, Buenos Aires, Argentina) and included native Spanish speakers. The investigation adhered to the principles of the Declaration of Helsinki. Patients and controls signed informed consent prior to their inclusion in the study. The study received approval from the ethics committee of the Hospital Municipal de Agudos (Bahía Blanca, Buenos Aires, Argentina).

2.1 | Participants

Patients with MCI and healthy controls underwent annual assessments from 2017 until 2020. Baseline assessment involved neurocognitive and eye-tracking evaluations. Follow-up assessment consisted of routine yearly clinical evaluations carried out by the referring practitioners.

A total of 65 MCI patients (mean age of 73 SD 6.1 years, mean years of education = 12) and 42 controls (mean age of 72 SD 6.7 years, mean years of education = 12) were enrolled in the study. Patients were diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria and relying on the classical MCI criteria,[16,17] which were applied by one psychiatrist and three neurologists. All MCI patients underwent a detailed clinical interview including medical history and physical examination and underwent neurological examination and blood testing. A comprehensive laboratory analysis was carried out to rule out other common pathologies. Patients were excluded at baseline if they: (1) had any medical conditions that could account for, or interfere with, their cognitive functioning; (2) had evidence of vascular lesions revealed on computed tomography (CT) or magnetic resonance imaging (MRI) scans; or (3) had evidence for an Axis I diagnosis (e.g., major depression or drug abuse) as defined by the DSM-IV. To be eligible for the study, patients had to have at least one caregiver providing regular care and support. A complete ophthalmologic exam was done before enrolling in the study. Those participants with a diagnosis of ophthalmologic diseases such as glaucoma, visually significant cataract, macular degeneration, or color vision problems were excluded from the study. Patients' visual acuity was 20/20 or corrected to 20/20. The Ishihara's test was used to rule out color blindness.

2.2 | Neurocognitive assessment

At baseline, we applied the Mini-Mental State Examination (MMSE),[18] the Addenbrooke's Cognitive Examination - Revised (ACE-R),[19] the INECO's Frontal Screen (IFR),[20] the Yesavage's Geriatric Depression Scale (GDS),[21] the Pfeffer Daily Activity,[22] and the Hamilton's Anxiety Scale.[23]

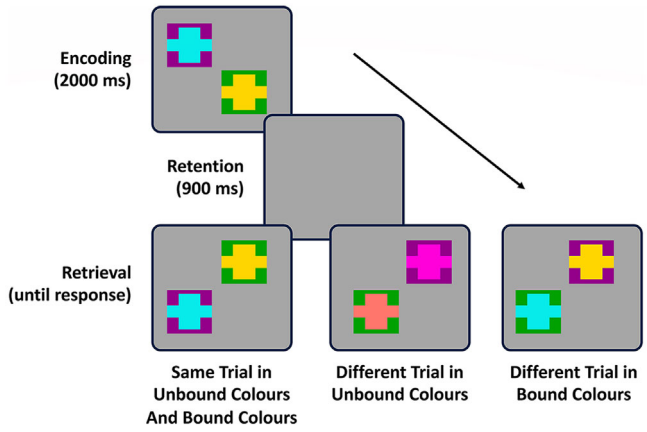

FIGURE 1 Example of trials for each test of the visual short-term memory binding (VSTMB) task.

2.2.1 | VSTMB task and eye movement

Visual stimuli were presented on the center line of a 19 LCD monitor (1024 × 768 pixels resolution). Participants sat at a distance of 60 cm from the monitor. Head movements were minimized using a chin rest. Eye movements (i.e., fixation duration and saccade amplitude) were recorded with a GazePoint eye tracker, with a sampling rate of 150 Hz. All recordings and calibration were binocular. During the task, participants were presented with arrays of object shapes in random positions on a 3 × 3 virtual grid, which sustained 10 degrees of visual angle. The stimulus was constructed following the layouts developed by Parra et al.[24] (Figure 1). The VSTMB/Eye-Tracking test took around 10 min to complete. (See Supplementary Material for an extended description.) Neurocognitive assessments and the VSTMB/Eye-Tracking test were performed on the same day. The total duration of a typical assessment session was 1.5 h (excluding MRI assessments). Participants were allowed to take as many breaks as they requested.

2.3 | Sample design and statistical analysis

Our first approach was aimed at corroborating the discriminative power of oculomotor behaviors to differentiate between MCI patients and Controls. To that aim, we defined an initial linear model comprising a between-subjects factor Group (Controls vs MCI patients) and a within-subject factors test (UC vs BC) and Memory Stage (Encoding vs Retrieval). Through annual clinical follow-up assessments, the referring consultants corroborated who among the MCI patients had progressed to a clinically defined ADS, remained as MCI, or progressed to another well-defined pathology, for example, Parkinson disease or frontotemporal dementia. The outcomes from such clinical decisions allowed us to define a second linear model comprising a between-subjects factor group (Controls vs MCI Stable vs MCI Converters to ADS vs MCI Converters to another pathology) and within-subject factors Condition (UC vs BC) and Memory Stage (Encoding vs Retrieval).

For each analysis, we implemented two models, one entering log Fixation Duration (in milliseconds) and one entering Saccade Amplitude (in degrees) as the dependent variables. In addition, we carried out a receiver-operating characteristic (ROC) analysis to determine the sensitivity and specificity of eye movements (i.e., log fixation duration and saccade amplitude) when performing the VSTMB task. Finally, to investigate the ability of oculomotor behaviors to prospectively predict dementia among MCI patients, we developed a model based on well-defined eye movement patterns.[12,25] Data from baseline assessment and blind to clinical decisions entered such a model to predict who among those with MCI would more likely progress to ADS and who would not. We were interested in contrasting the outcomes from clinical decisions and those from such a prediction model. Statistical analyses were performed in R version 3.1.1 (RDevelopment Core Team). Group differences in the VSTMB task were tested with analysis of variance (ANOVA) and linear regression.

2.4 | Procedures

After reading the information sheet and signing the consent form, participant assessments were administered in the following order: (1) The VSTMB/Eye-Tracking task, (2) MMSE, (3) ACE-R, (4) IFR, (5) Yesavage's GDS, (6) Pfeffer daily activity, and (7) The Hamilton's Anxiety Scale. There was finally a debriefing session where the participant's questions were answered.

3 | RESULTS

3.1 | Neurocognitive test

At Baseline, the mean score of MCI patients on the MMSE was 26.6 (SD = 2.2) versus 29.7 (SD = 0.4) in Controls; cutoff point for MCI was 24. MCI patients score on ACE-R was 78.3 (SD = 10.8) versus 93.2 (SD = 0.8) in Controls; the cutoff point for MCI was 86. Performance on the IFR revealed a mean score of 18.4 (SD = 5.2) for MCI patients versus 27.0 (SD = 1.1) in Controls; the cutoff point was 25. The mean score on the GDS in MCI was 8.5 (SD = 2.8); the cutoff point for depression was 9. The Pfeffer daily activity in MCI was a mean score of 6.1 (SD = 1.5), cutoff of 6, and the Hamilton's Anxiety Scale in MCI was a mean score of 16.3 (SD = 3.5), with a cutoff of 18. Therefore, our sample of MCI did meet classical criteria (see also[3]).

3.2 | Discriminating between MCI and healthy controls

To test our initial hypothesis (i.e., discriminative power of oculomotor behaviors to distinguish between MCI patients and Controls) we ran our first linear model comprising a between-subjects factor Group (Controls vs MCI patients) and within-subjects factors Condition (UC vs BC) and Memory Stage (Encoding vs Retrieval).

TABLE 1 Parameter estimates for fixed effects of Linear Models for log Fixation Duration **(A)** and Saccade Amplitude **(B)** when comparing MCI and Controls across tasks and memory stages

	log Fixation Duration				Saccade Amplitude		
(A)	**M**	**SE**	***t*-value**	**(B)**	**M**	**SE**	***t*-value**
Fixed effects				**Fixed effects**			
Mean log Fixation Duration	5.31	0.00	**750.70**	Mean Saccade Amplitude	2.35	0.05	**45.86**
Group x Task x Encoding				**Group x Task x Encoding**			
Control vs MCI X BC	-0.33	0.00	**-42.11**	Control vs. MCI X BC	1.09	0.05	**18.93**
Control vs MCI X UC	-0.28	0.00	**-37.72**	Control vs. MCI X UC	0.81	0.05	**14.90**
Group x Task x Retrieval				**Group x Task x Retrieval**			
Control vs MCI X BC	-0.20	0.00	**-21.75**	Control vs. MCI X BC	1.14	0.06	**16.82**
Control vs MCI X UC	-0.14	0.00	**-16.60**	Control vs. MCI X UC	0.64	0.07	**16.72**

Threshold of significance is set at t = ±1.95.

3.2.1 | Behavioral data

Our first two-way mixed ANOVA revealed a significant Group by Condition interaction ($F = 123.7$, $p < 0.001$). Relative to Controls, MCI showed poorer performance on the BC condition (63% and 91% correct responses for MCI and controls, respectively) and a smaller difference during the UC condition (72% and 88% correct responses for MCI and controls, respectively). Four Bonferroni corrected post hoc comparisons, two across groups (i.e., UC: MCI vs controls and BC: MCI vs controls) and two across conditions (MCI: UC vs BC and controls: UC vs BC) were carried out to further investigate the interaction (corrected p-value = 0.0125). They revealed that patients in the ADS group performed significantly poorer than Controls on the BC ($t = 112.2$, $p < 0.001$), and their own performance on the UC condition ($t = 15.8$, $p < 0.001$). Thus, it was the impairment in the patient's ability to bind colors together that led to the significant interaction.

3.2.2 | Eye movement data

Fixation duration

Table 1A and Figure 2A present fixation duration data across Group (MCI vs controls), Condition (BC vs UC), and Memory Stages (Encoding vs Retrieval). As shown in Table 1A and in Figure 2A, the log mean fixation duration was significantly shorter in MCI than in Controls, when considering the encoding phase of the BC condition ($t = -42.11$ and $t = -37.72$, BC and UC, respectively). When considering the retrieval phase, MCI and Controls showed again significant differences in their fixation durations, being the shortest ones on the BC condition ($t = -21.75$, $t = -16.60$, BC and UC, respectively).

Saccade amplitude

When considering saccade amplitudes, MCI had longer saccades than Controls while encoding BC and UC, with the difference more pronounced in the BC condition ($t = 18.93$ and $t = 14.90$, respectively). When comparing MCI and controls during retrieval, the former group showed again longer saccades while performing the BC condition, although the significance reached by both tasks was similar ($t = 16.82$ and $t = 16.72$, respectively) (see Table 1B and Figure 2B).

3.3 | Predicting MCI to ADS conversion

To test the hypothesis that behavioral and oculomotor data would predict conversion from MCI to ADS, we ran a second linear model. This comprised a between-subjects factor Group that was defined based on clinical decisions (Controls vs MCI Stable vs MCI Converters to ADS vs MCI Converters to other pathology) and two within-subject factors, Test (UC vs BC) and Memory Stage (Encoding vs Retrieval) (see Supplementary Material, Contrasting prediction models, for two models attempted to test this hypothesis).

3.3.1 | Behavioral data

Group comparisons showed that MCI patients who converted to ADS (MCI_C) performed significantly worse on the BC test than MCI Stable (MCI), and MCI who progressed to another pathology (MCI_O), being the Group by test and their interaction significance ($F = 11$, $p < 0.001$). Finally, when performing the UC test there were no significant differences between MCI subgroups. These results mirror those reported by[14] and more recently by.[12] Three corrected post hoc comparisons across tests (MCI: UC vs BC, MCI_O: UC vs BC, and MCI_C: UC vs BC)

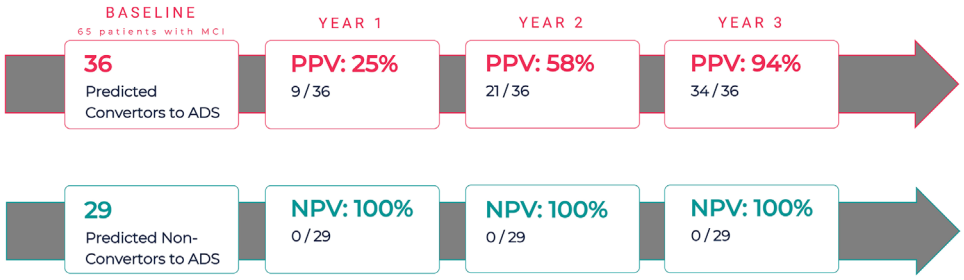

FIGURE 2 Diagram illustrating the outcomes from our prediction model applied to baseline data and from clinical decisions made during follow-ups.

TABLE 2 Parameter estimates for fixed effects of Linear Models for log Fixation Duration **(A)** and Saccade Amplitude **(B)** when comparing MCI, MCI_O, MCI_C, and Controls (C) across tasks and memory stages

	log Fixation Duration				Saccade Amplitude		
(A)	**M**	**SE**	***t*-value**	**(B)**	**M**	**SE**	***t*-value**
Fixed effects				**Fixed effects**			
Mean log Fixation Duration	5.28	**0.00**	795.88	Mean Saccade Amplitude	2.63	**0.04**	54.19
Group x Task x Encoding				**Group x Task x Encoding**			
Control vs MCI_O X BC	-0.16	**0.012**	-13.42	Control vs. MCI_O X BC	0.89	**0.09**	9.72
Control vs MCI_O X UC	-0.14	**0.01**	-11.78	Control vs. MCI_O X UC	0.53	**0.08**	5.97
Control vs MCI X BC	-0.27	**0.00**	-29.32	Control vs. MCI X BC	1.01	**0.06**	14.85
Control vs MCI X UC	-0.23	**0.00**	-25.55	Control vs. MCI X UC	1.05	**0.06**	15.92
Control vs MCI_C X BC	-0.42	**0.00**	-48.86	Control vs. MCI_C X BC	1.22	**0.06**	19.01
Control vs MCI_C X UC	-0.35	**0.00**	-43.24	Control vs. MCI_C X UC	0.73	**0.06**	12.15
Group x Task x Retrieval				**Group x Task x Retrieval**			
Control vs MCI_O X BC	-0.26	**0.01**	-20.33	Control vs. MCI_O X BC	0.88	**0.09**	9.60
Control vs MCI_O X UC	-0.14	**0.01**	-11.46	Control vs. MCI_O X UC	0.70	**0.08**	7.97
Control vs MCI X BC	-0.35	**0.01**	-35.13	Control vs. MCI X BC	1.37	**0.07**	18.48
Control vs MCI X UC	-0.29	**0-00**	-31.16	Control vs. MCI X UC	1.33	**0.06**	19.10
Control vs MCI_C X BC	-0.54	**0.00**	-54.96	Control vs. MCI_C X BC	1.07	**0.07**	14.82
Control vs MCI_C X UC	-0.40	**0.00**	-43.70	Control vs. MCI_C X UC	0.96	**0.06**	14.20

Threshold of significance is set at t = ±1.95.

were carried out to further investigate the interactions (corrected *p*-value = 0.0125). They revealed that patients in the MCI_C, MCI, and MCI_O groups performed significantly worse on the BC than they performed on the UC test (MCI_C vs MCI: $p < 0.0001$, MCI_C vs MCI_O: $p < 0.0001$, and MCI vs MCI_O $p < 0.002$), with MCI_C the most impaired group.

3.3.2 | Eye movement data

Fixation duration

Table 2A and Figure 3A present fixation durations data across Groups, Task, and Memory Stages. Significant effects observed during the encoding phase were driven by longer fixation durations in Controls, relative to MCI and MCI_C but not to MCI_O, which were more prominent on the BC test ($t = -29.32$, $t = -48.86$, $t = -13.42$, respectively) than on UC test ($t = -25.55$, $t = -43.24$, $t = -11.78$, respectively). Similar results were found during the retrieval phase, where Controls produced longer fixations than MCI_O, MCI and MCI_C on the BC ($t = -20.33$, $t = -35.13$, $t = -54.96$, respectively) and UC ($t = -11.46$, $t = -31.16$, $t = -43.70$).

Post hoc analysis contrasting tests across Group showed that only Controls displayed a significant positive difference between BC and UC (BC > UC) while comparing encoding fixations. When considering retrieval, fixation duration during the BC showed the pattern Controls > MCI_O > MCI > MCI_C. Post hoc analysis contrasting groups across tests showed that discrepancies in fixation duration were present across memory stages, with those recorded during the encoding of BC following the pattern MCI >MCI_O > MCI_C (see Supplementary Material for the full set of pairwise contrasts). Taken together, these

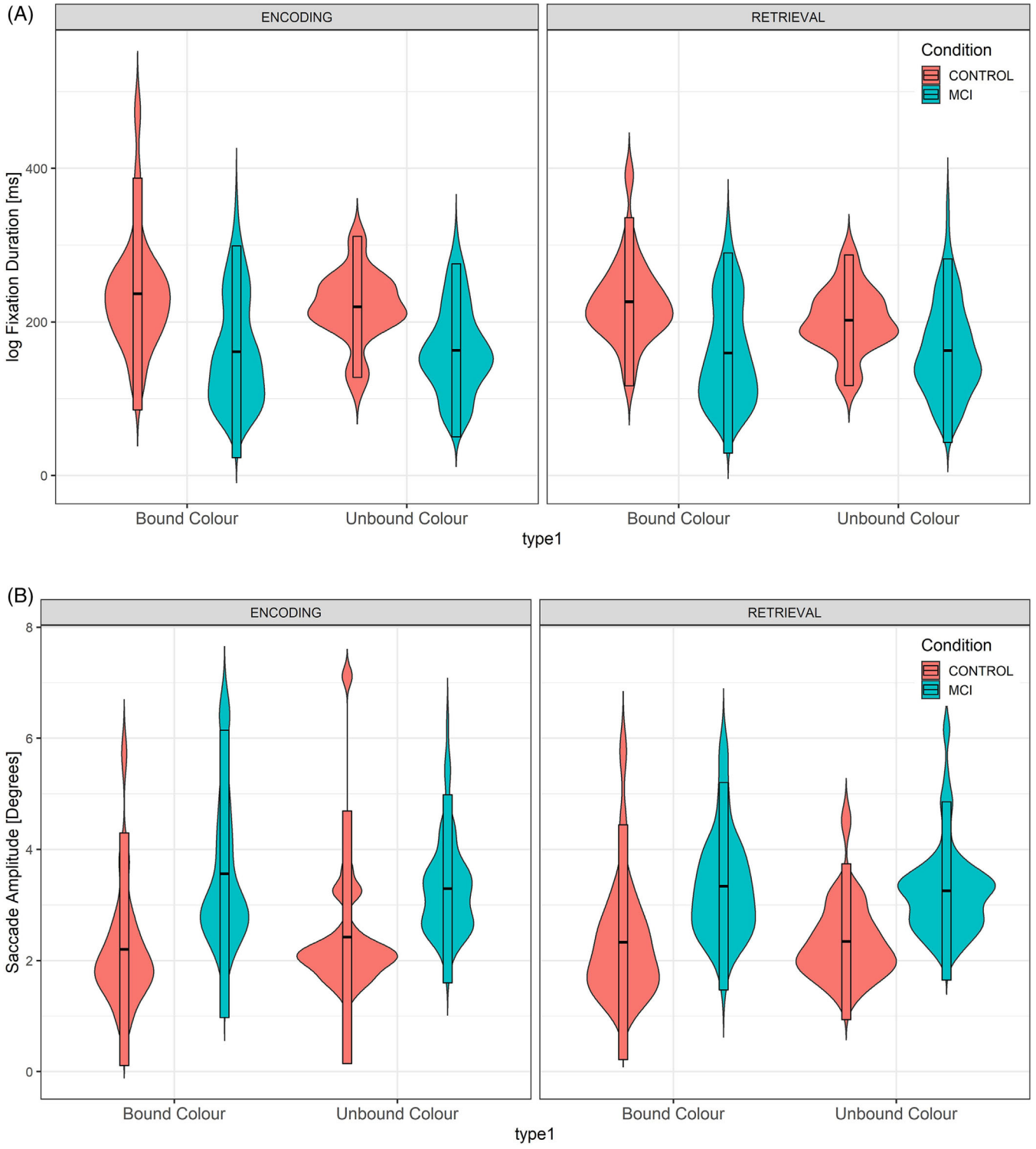

FIGURE 3 (A) Effect of a binding task on log fixation duration in miliseconds (ms) in control and in MCI patients during Encoding and Retrieval moments. (B) Effect of binding task on saccade amplitudes in degrees in control and in MCI patients during Encoding and Retrieval moments. The boxplots inner the violin plot show the minimum, first quartile, median, third quartile, and maximum. The probability density function (PDF) shows the shape of the data set. A wider PDF indicates that the value occurs more frequently, and a narrower density function indicates that the value occurs less frequently.

results suggest that the demands posed by the BC test during the encoding phase of the VSTMB task, as informed by fixation duration, were hardly met by MCI patients, and with those in the MCI_C category experiencing the greatest challenge.

Saccade amplitude

Table 2B and Figure 3B present Saccade Amplitude data across Groups, Task, and Memory Stages. A similar pattern was observed for this oculomotor behavior. A small difference was found during the encoding of BC when comparing Controls versus MCI_O, followed by differences between Controls versus MCI, and Controls versus MCI_C ($t = 9.72$, $t = 14.85$, $t = 19.01$, respectively). Similar effects were found during the UC test ($t = 5.97$, $t = 15.92$, $t = 12.15$, respectively) during encoding, although to a lesser extent. Finally, saccade amplitude was again longer in the three MCI groups relative to Controls on both the BC ($t = 9.60$, $t = 14.82$, $t = 18.48$, respectively) and UC test ($t = 7.97$, $t = 14.20$, $t = 19.10$, respectively). Post hoc analysis contrasting tests across Groups showed that only Controls and MCI displayed negative significant differences between their saccade amplitudes during the encoding phase of BC and UC. Finally, post hoc analysis contrasting Groups across tests showed significant differences during encoding and retrieval, with those observed during encoding of BC being larger than those observed during UC, particularly in MCI_C (see Supplementary Material, Further post hoc analyses, for the full set of pairwise contrasts). As for Fixation Durations, Saccade Amplitude revealed more oculomotor impairments (larger amplitudes) during the encoding phase of the BC test of the VSTMB task in MCI patients who progressed to ADS during the study than in those who progressed to other pathologies or remained stable.

As both Fixations Durations and Saccades Amplitudes proved able to discriminate between not only Controls and MCI generally but also between MCI subgroups, we used aggregate subject-based summaries of eye movement measures to predict group membership using ROC analysis. This analysis aimed to determine whether oculomotor behaviors were able to differentiate MCI_C from MCI and from MCI_O. The analysis revealed that our eye-tracking metrics achieved 95% sensitivity and 95% specificity to distinguish between MCI and MCI_C patients (area under the curve [AUC] = 0.95). When distinguishing between MCI and MCI_O, the sensitivity was 60% and the specificity was about 75% (AUC = 0.60). Finally, when distinguishing between MCI_C and MCI_O, the sensitivity was 100% and the specificity was 100% (AUC = 1) (see Figure 4).

3.4 | Convergence of research and clinical evidence

As mentioned in Methods, MCI subgroups were defined based on clinical decisions. To investigate the ability of oculomotor behaviors to prospectively predict MCI progression, baseline data were entered into a prediction model. The outcomes from such models, contrasted with clinical decisions, are shown in Figure 5. The model predicted that of the 65 MCI patients, 36 would likely progress to ADS, whereas the rest would not progress to this form of dementia. The analysis revealed that by year 1, 25% (i.e., 9 of 36 MCI) of those MCI the model predicted would convert to ADS met diagnostic criteria.[26] At year 2, 21 of 36 MCI had progressed to ADS (58%) and at year 3, 34 of the 36 identified as potential ADS converters (94%) met diagnostic criteria. Of the 29 patients that the model predicted would not progress to ADS, 5 developed frontotemporal dementia, 2 developed Parkinson disease, 4 developed vascular dementia, 7 had major depression, and 11 remained as MCI.

4 | DISCUSSION

The present study was to investigate the hypothesis that a cognitive biomarker that combines eye-tracking measures collected while people perform the VSTMB task would accurately predict who among the MCI patients would more likely progress to the AD clinical syndrome (ADS). Our results confirmed such a hypothesis. Prospective prediction models demonstrated that 94% of MCI patients whose baseline cognitive biomarker profile suggested a risk for progression did meet ADS criteria in successive follow-ups. However, none of those whose cognitive biomarker profile were incompatible with AD risk progressed to this form of dementia. ROC analysis confirmed the high level of sensitivity and specificity of this novel cognitive biomarker investigated in a longitudinal cohort.

Our results confirm that Fixation Duration and Saccade Amplitude are strongly affected in MCI patients while performing the VSTMB task, in particular in those who will convert to ADS. VSTMB declines in patients with dementia due to AD and in those who will inevitably develop dementia due to familial AD but are still asymptomatic as demonstrated by traditional neuropsychological tasks.[13] VSTMB is an integrative memory function known to support the conjunction of features necessary to create an object's identity.[14] Parra and collaborators recently showed that VSTMB deficits in patients in the prodromal stages of familial AD are associated with altered patterns of brain connectivity, which seem to involve not only parietal-occipital regions but also the frontal lobes.[27,28,29] More recently, the association of VSTMB with the accumulation of Aβ in preclinical and clinical AD[30,31] has been confirmed.

Because there is a close relationship between eye movements and cognition,[32] and the existing evidence demonstrates that visual processing is impaired in AD, with visual exploration and information extraction during fixations being less organized.[25] Changes in eye movement patterns can be used to infer MCI changes in cognitive processes and potential conversion to AD.[33] Previous research[34,35,36] has suggested that patients with neurodegenerative disorders characterized by cognitive impairments (e.g., AD, Parkinson disease, and Lewy body dementia) display longer fixation durations than controls while processing daily living complex tasks (e.g., reading sentences, determining the time from a clock, recognizing objects). This evidence suggests that neurodegeneration could impair visual processing and that such impairment could be an early manifestation of AD. Our data shows that Fixation Duration produces a different pattern when comparing Controls and MCI, in that MCI produces shorter fixation

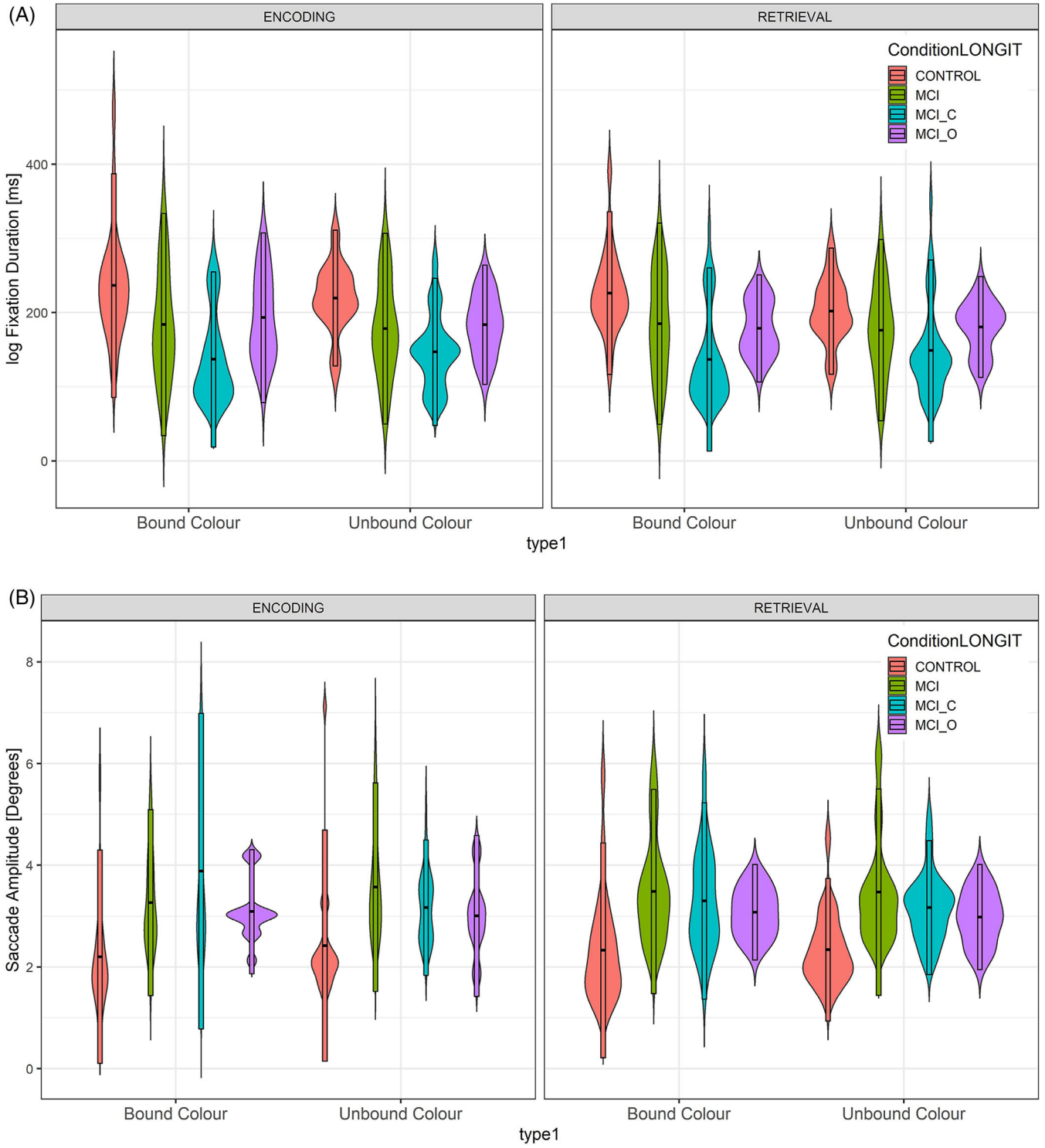

FIGURE 4 (A) Effect of binding task on log fixation duration in control and in MCI, MCI_C, and MCI_O patients during Encoding and Retrieval moments. Fixation duration is plotted on log milliseconds (ms). (B) Effect of binding task on saccade amplitudes in degrees in control and in MCI, MCI_C, and MCI_O patients during Encoding and Retrieval moments. The boxplots inner the violin plot show the minimum, first quartile, median, third quartile, and maximum. The probability density function (PDF) shows the shape of the data set. A wider PDF indicates that the value occurs more frequently, and a narrower density function indicates that the value occurs less frequently.

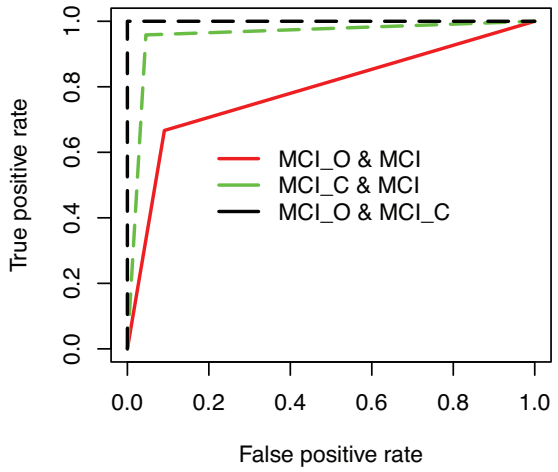

FIGURE 5 **ROC Analysis.** ROC analysis with performance on saccade amplitude and fixation duration during VSTMB task for MCI, MCI_O, and MCI_C patients.

durations than Controls when encoding and retrieving both BC and UC (see Figure 2A). Controls displayed the longest fixations during the encoding of BC. This suggests that, relative to UC, this task poses additional cognitive demands,[32,35] which MCI patients, particularly MCI_C, failed to meet (see Figure 3A).

The relationship between saccade amplitude and the complexity of the visual stimulus or task has been documented.[36,37] Mosimann et al.[36] proposed that the occipito-temporal network is important for central vision and for the generation of small saccades, and the occipitoparietal network for spatial global vision and the generation of long saccades.[38,39,40] An imbalance between the two networks with a relatively lower occipitotemporal dysfunction and a more pronounced occipitoparietal dysfunction, may lead to predominantly longer saccade amplitudes and shorter fixations during exploration. Prvulovic et al.[41] found a reduced parietal activation and increased temporal activation during visuospatial processing in AD patients. In our study, MCI produce longer saccades and shorter fixation durations when comparing to controls (in particular those eye movements coming from MCI_C), suggesting as proposed by Mosimann et al.[36] a potential impaired occipitoparietal network. In fact Parra et al.[37] have demonstrated previously that VSMTB relies on a network that involves occipitotemporal and posterior parietal regions.

The performance of our healthy controls cohort on the BC test of the VSTMB task was comparable with that of previous reports, suggesting that more demanding tasks would produce shorter saccades.[32] Previous studies have established close links between saccade preparation and sensory encoding, and between covert attention and visual memory performance.[42,43] MCI patients, in general, produced longer saccades on both encoding and retrieval when compared with controls (see Figure 2B). Furthermore, MCI_C produced longer saccades and shorter fixation durations when processing BC, suggesting less-efficient oculomotor behaviors linked to the exploration and identification of color combinations. As the behavioral data confirmed, such oculomotor behaviors did not lead to successful performance.

Of key relevance to our study, we found that eye movements can predict conversion from MCI to ADS. Eye movements were able to distinguish MCI patients from MCI_C with 95% sensitivity and 95% specificity. Although the results presented support this prediction, they also open new questions. For instance, although we followed up with our patients for 40 months, it is still possible that some MCI patients from either group (MCI or MCI_O) may progress to ADS over the next months and years. Further follow-ups will be necessary to ascertain their final diagnosis. Moreover, as we did not have access to the biomarkers for AD recently recommended,[26] we adhered to the recommendations of the consensus group and used the term ADS based on clinical decisions. Some of the patients enrolled in this study had undergone MRI assessments, and we were able to analyze the MRI results for a sub-section of the patients. The Supplementary Material shows based on neuroimaging data that these patients had patterns of brain atrophy compatible with the (N) component of the A/T/N framework. Nevertheless, future studies are needed to validate the cognitive biomarkers here proposed against pipeline AD biomarkers.

The correlation between model-based and clinical-based decisions regarding the progression to ADS is worth highlighting. The ability of oculomotor behaviors recorded during the VSTMB task to predict conversion to ADS among MCI patients using baseline data was well aligned with the outcomes from successive clinical follow-ups. Our current data suggest that those patients predicted to progress to ADS and later classified as MCI_C displayed baseline behaviors (oculomotor and memory scores) compatible with those reported previously in AD samples.[12] Our data suggest that our cognitive biomarker can accurately identify up to 40 months in advance of MCI patients who will embark on different trajectories (i.e., MCI_O or MCI_C).

5 | CONCLUSIONS

Our results confirmed that MCI patients produced eye movements patterns while they performed a task considered a marker for AD, differently from those produced by healthy controls. MCI_C showed abnormal saccades and fixation durations, suggesting major impairments in their cognitive functions, for example, in memory and executive functions. We feel compelled to propose that oculomotor responses during the performance of the VSTMB task may be considered a preclinical digital biomarker for AD. Such an affordable and non-invasive biomarker will aid in the identification of early symptoms and help monitor the disease progression. As a screening tool, this method can support clinical practice in underserved countries, which are expected to be severely impacted by dementia. Furthermore, prevention trials will greatly benefit from this tool as it will increase certainty during recruitment (i.e., Aβ positive and tau positive) and be used to measure the impact of treatment on cognitive domains.

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CONFLICT OF INTEREST

Mario A Parra: Chief Neuroscientific Officer of ViewMind. Juan Granada: No conflicts of interest to disclose. Gerardo Fernández: Chief Scientific Officer of ViewMind.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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