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Effect of advancing age on event-related potentials (P300) measures

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Abstract

Background Aging has been defined as a persistent deterioration in the age-specific fitness components of an organism, attributed to internal physiological degeneration. Cognitive abilities, encompassing attention, memory, executive cognitive functions, language, and visuospatial capacities, are distinctive domains affected by aging. Numerous studies have documented measurable effects on these cognitive domains, indicating a discernible decline in their functionality with advancing age. Cognitive impairment often unfolds insidiously, remaining clinically silent for extended periods. Age, as a critical factor, exerts a notable influence on P300 measures.

Result Spearman rank correlation was calculated between age and P300 measures. In group 1A (age range of 10–20 years), we found a strong positive correlation between age and amplitude of P300 ($r = 0.96$, $p < 0.001$), while a weak correlation was found between latency and age. In group IB (age range: 21–40 years), a moderate negative correlation ($r = -0.43$, $p < 0.05$) was found between age and amplitude of P300, while a strong positive correlation ($r = 0.87$, $p < 0.001$) was obtained between age and latency. In group 2A (age: 41–60 years), it was found that amplitude has a strong negative correlation ($r = -0.97$, $p < 0.001$) with age, while latency has a strong positive correlation ($r = 0.89$, $p < 0.001$). In group 2B (age: 61–80 years), it was found that amplitude has a strong negative correlation ($r = -0.93$, $p < 0.001$) with age, while latency has a strong positive correlation ($r = 0.95$, $p < 0.001$).

Conclusion In this study, it is concluded that amplitude of P300 decreases and latency increases with increasing age.

Keywords P300, Aging, Hearing loss, Event-related potentials

Background

Aging has been defined as a persistent deterioration in the age-specific fitness components of an organism, attributed to internal physiological degeneration [1]. On attaining reproductive maturity by an organism, aging manifests itself as a universal, progressive, and inherent decline. There is variation in classifying old age across the globe, with affluent nations characterizing it at around 60 to 65 years, whereas, in developing nations marked by lower life expectancies, the onset of old age is observed much earlier. The aging process is accompanied by a multitude of structural and functional transformations within the human body. Advancing age establishes an inverse relationship with the efficiency of various physiological systems. As age increases, there is a discernible escalation in the incidence and prevalence rates of diverse diseases and disorders [2]. Notably, aging is intricately associated with the cognitive abilities of humans. A substantial decline in cognitive functioning has been consistently reported as age progresses.

Cognitive abilities, encompassing attention, memory, executive cognitive functions, language, and visuospatial capacities, are distinctive domains affected by aging [3]. Numerous studies have documented measurable effects on these cognitive domains, indicating a discernible decline in their functionality with advancing age. The ramifications of aging extend beyond mere chronological

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markers, exerting considerable influence on the intricate cognitive landscape of the human experience.

The assessment of cognitive abilities in individuals is a markable work within the realm of psychology, and various tests have been developed for the same. One such widely utilized measure, particularly in the field of audiology, is the auditory P300 test. This assessment tool is extensively used due to its efficacy in evaluating cognitive functions.

Event-related potentials (ERPs) constitute minute electrical voltages originating in the brain in response to specific stimuli or events. Among the plethora of event-related or endogenous evoked responses, the P300 wave stands out as one of the earliest identified auditory responses. The P300 response is essentially a constituent within an extended auditory late response (ALR) time frame, typically recorded under specific stimulus conditions [4]. Its elicitation often involves the utilization of an odd-ball paradigm, where a frequent stimulus and a less common or rare stimulus are presented to evoke the P300 response. Crucially, the emergence of the P300 wave hinges on the active engagement of the subject in the task of detecting the presented targets. In the odd-ball paradigm, various parameters such as frequency, intensity, or duration of the stimulus are manipulated to differentiate between the two stimuli [5]. The hippocampus, responsible for short-term memory functions, plays a pivotal role in triggering the P300, and its occurrence is intricately linked to internal cognitive processes [6, 7]. Intracranial investigation, studies with patients with focal brain lesions, and functional neuroimaging (fMRI) studies converge with scalp-recorded event-related potential (ERP) data suggest that main regions consistently attributed to generating detection-related brain activation include the temporal-parietal junction, medial temporal complex, and the lateral prefrontal cortex. Notably, some researchers observed the absence of P300 in individuals with unilateral cortical lesions, particularly in the posterior superior temporal plane, suggesting the significance of the temporal-parietal junction in P300 generation in humans [8]. The P300 response exhibits its highest amplitude over the centro-parietal regions near the midline, with fluctuations in amplitude reflecting the likelihood of target stimuli. The latency of the P300 response is influenced by the subject's ability to discriminate the target stimulus from standard stimuli, with an average latency of 300 ms in young adults performing a basic discrimination task.

Furthermore, individuals with reduced cognitive function exhibit smaller P300 amplitudes and delayed latencies compared to age-matched normal participants. The calculation of P300 amplitude involves measuring from the N1 peak to the P300 peak, while the latency is determined within the time window of the P300 peak. Normative values for P300 amplitude range from 1.7 microvolts to 20 microvolts, and the latency spans from 250 to 500 ms [9–13]. These quantitative metrics serve as reference points for assessing and interpreting the P300 wave in cognitive and auditory studies.

Age emerges as a paramount determinant influencing P300 latency, with a discernible impact on both amplitude and latency, particularly among individuals over 40 [14, 15]. A study led by Polich J et al. revealed a notable increase in P300 latency, reaching up to 65 ms within the age range of 20 to 70 years [16]. Similarly, Yamashita et al., in their investigation, identified a significant positive correlation between age and P300 latency, with an approximate increase of 1.7 ms per year, accentuated after the age of 60. Intriguingly, the correlation between age and P300 amplitude manifested prominently at the Pz location ($p < 0.05$) [17]. García de la Cadena et al. conducted a study focusing on the Mexican population, involving 106 participants spanning an age range of 20 to 100 years. Their findings indicated a consistent increase in latency, at a rate of 0.38 ms per year, alongside a decline in amplitude at a rate of 0.20 mV per year [18]. A comprehensive systematic review and meta-analysis by van Dinteren et al. shed light on the maturational trajectory of P300 latency and amplitude from childhood to adolescence, reaching a plateau before the onset of degenerative effects [19].

Furthermore, a study by Puttabasappa et al. underscored the age-related alterations in P300 characteristics. Their investigation demonstrated an age-related increase in P300 latency, coupled with a significant reduction in P300 amplitude across various age groups, with the exception of the 60–70 years age group [20].

In essence, these studies collectively emphasize the intricate relationship between age and P300 measures, elucidating the nuanced patterns of change in latency and amplitude across the lifespan. The observed variations contribute to a deeper understanding of the age-associated dynamics within the cognitive and auditory domains.

Cognitive impairment often unfolds insidiously, remaining clinically silent for extended periods. Consequently, diagnoses tend to occur late in the disease course, diminishing the efficiency and success of therapeutic interventions. Age, as a critical factor, exerts a notable influence on P300 measures. With increasing age, there is a systematic augmentation in P300 latency accompanied by a decrement in amplitude. Brain maturation plays a pivotal role in eliciting the P300 response, especially in developing children. While existing studies predominantly originate from foreign countries, a notable gap exists in the literature pertaining to the

Indian population. This study seeks to address this gap by exploring the specific effects of age on P300 measures within the Indian context. By doing so, it aims to contribute valuable insights into the understanding of age-related cognitive dynamics in a population that is often underrepresented in the current body of research.

Method

Study settings

This study has been performed in the Department of Audiology, Ali Yavar Jung National Institute of Speech and Hearing Disabilities (Divyangjan), Mumbai, for a duration of 11 months from January 2023 to November 2023. The study was approved by the Institutional Ethical committee. This is a survey research design. The samples were collected by purposive sampling techniques.

Participants

A total of 113 participants were tested, but 90 participants were included for this study, spanning an age range from 10 to 79 years ($M=45.18$; *S.D*,20.41). Out of these participants, 12 were excluded due to not meeting the criteria of normal hearing, and 11 participants were excluded due to poor wave morphology. To systematically examine the impact of age on P300 measures, participants were categorized into two main groups based on age range.

Group 1: Participants aged between 10–40 years, further subdivided into two sub-groups.

- Subgroup 1A ($N=12$): Participants aged between 10 and 20 years.
- Subgroup 1B ($N=26$): Participants aged between 21 and 40 years.

Group 2: Participants aged between 41 and 80 years, also divided into two sub-groups.

- Subgroup 2A ($N=27$): Participants aged between 41 and 60 years.
- Subgroup 2B ($N=25$): Participants aged between 61 and 80 years.

All participants exhibited normal hearing in both ears, as indicated by a pure tone average (PTA) of less than 25 dBHL at 500 Hz, 1000 Hz, and 2000 Hz frequencies. Selection criteria further ensured that participants had no abnormalities in speech and language abilities, and showed no signs of neurological, sensory-motor, cognitive, or behavioral impairments. The careful selection of participants with normal hearing and absence of additional abnormalities aimed to establish a homogeneous sample, providing a solid foundation for investigating age-related variations in P300 measures with minimized confounding factors.

Instrumentation and materials

Otoscope

An otoscope was employed to visually inspect the ear canal and tympanic membrane. This step ensured a thorough examination of the external auditory structures for any potential abnormalities.

Resonance dual-channel audiometer

Pure tone audiometry was conducted using a resonance dual-channel audiometer. This instrument allowed for precise measurement of hearing thresholds across various frequencies, providing essential data on participants' hearing acuity.

GSI Tympstar Pro Tympanometer

The middle ear function of participants was evaluated using the GSI Tympstar Pro Tympanometer. This instrument facilitated the assessment of tympanic membrane compliance and middle ear pressure.

Neurosoft instrument

The P300 test was performed using a Neurosoft instrument. This specialized equipment allowed for the measurement and analysis of P300 responses to tone burst stimuli.

Materials

Addenbrooke's Cognitive Examination III

The Addenbrooke's Cognitive Examination III, a comprehensive screening test, was administered to participants. This test, encompassing attention, memory, language, orientation, visual perceptual, and visuospatial assessments, took approximately 15–20 min. Individuals who successfully passed this cognitive screening were included in the study. Scoring involved assessing performance in domains such as attention, memory, fluency, language, and visuospatial skills, with an overall score derived from the summation of these individual domain scores [21].

P300 stimulus

Tone burst stimuli at different frequencies (1 kHz and 2 kHz) were employed to elicit P300 responses. The target stimuli, representing rare, abnormal, and uncommon auditory events, were delivered at 2 kHz with an intensity level of 30 dB SL. Baseline stimuli, or frequent stimuli, were presented at 1 kHz and 30 dB SL. The oddball paradigm was implemented, randomly introducing

uncommon stimuli. Participants were instructed to focus on the rare stimuli, forming the basis of the P300 assessment.

Procedure

Written consent was taken from each participant outlining the purpose, procedures, and potential risks of the study. A detailed case history was systematically collected from each participant. The information encompassed various aspects such as the history of hearing loss, potential causes of hearing impairment, handedness, and relevant medical history. Participants with a history of left-handedness or conductive hearing loss were excluded from the study.

Following the case history, otoscopic examination was conducted. Participants underwent the Addenbrooke's Cognitive Examination III, a comprehensive cognitive screening test. Participants who successfully passed this cognitive screening were included in the study. It is noted that none of the participants failed the screening.

Pure tone audiometry (PTA)

Pure tone audiometry was conducted using a Resonance R37a clinical audiometer. The evaluation took place in a sound-treated two-room setup, adhering to noise level standards within permissible limits (ANSI S3.1). Pure tone air conduction and bone conduction thresholds were determined for octave frequencies ranging from 250 to 8000 Hz. The TDH-39 circumoral transducer was used for air conduction, and a B-71 bone vibrator was used for bone conduction.

Tympanometry

Tympanometry was carried out utilizing the GSI Tympstar Pro instrument at a 226 Hz probe tone. Participants exhibiting only "A" type tympanograms were included in the study.

P300 test

The P300 test was conducted in a quiet room where participants were comfortably seated. Electrode placement sites were prepared using Neuoprep solution, and 10–20 conduction gel was applied to optimize electrode conductivity. Electrodes were affixed using microporous adhesive tape, with an accepted impedance of up to 5 kΩ. Electrode positions included Cz for the non-inverting electrode, M1/M2 for the inverting electrode, and Fpz for the ground. The low-pass filter settings were 50 Hz, high-pass filter settings were kept at 0.01 Hz, and the notch filter was turned off to preserve important frequencies. A total of 400 sweeps were used for data acquisition, with parameters detailed in Table 1.

Table 1 Parameters used to elicit P300

Parameters	Value
Stimulus type	Tone burst
Analysis epoch	250–700 ms
Non-meaningful tone	30 dBSL
Rare or meaningful tone	30 dBSL
Filters: High-pass cutoff	50 Hz
Low-pass cutoff	0.1 Hz
Frequency of meaningful tone	2000 Hz
Frequency of non-meaningful tone	1000 Hz
Probability of target tone	20%
Transducer type	Insert earphone: Er-3A
Rate of stimuli	1.1/s
Polarity	Alternating
Amplification	75,000

Subject instruction

Participants were instructed that they would hear a continuous beep-like sound with infrequent high-frequency sounds interspersed. Their task was to pay attention to the infrequent sound and press a button simultaneously.

Identification of latency and amplitude of P300

Analysis of the P300 waveform involved an averaging process. A minimum of two tracings for both infrequent and frequent stimuli were recorded per patient to enhance reliability. Tracings were averaged, and the wave with the highest positive peak post the N1-P2-N2 complex was selected. Latency measures were determined at the center of the peak, while amplitude measures were taken at the location of the largest slope in the peak. Latency reference values ranged from 225 to 265 ms, and amplitude reference values ranged between 5 and 20 μV. Amplitude was marked from the N2-P3 waveform.

Results

The data collected for the study were subjected to statistical analysis using SPSS (26 version) software. Descriptive statistics were calculated for both groups. Initially, the Shapiro–Wilk test for normality was applied to assess if the data adhered to normal distribution assumptions. Given the violation of the normality assumption ($p < 0.05$) for stimuli, non-parametric tests were employed for the analysis of the age-related effects on P300 measures.

Table 2 Descriptive statistics of P300 measures

P300 measures		10–20 years	21–40 years	41–60 years	61–80 years
P300 Amplitude (μv)	Mean	5.73	7.24	6.04	3.86
	Standard deviation	0.46	0.60	0.38	0.49
P300 latency (ms)	Mean	259.87	311.60	318.26	345.66
	Standard deviation	4.02	4.86	2.49	10.32

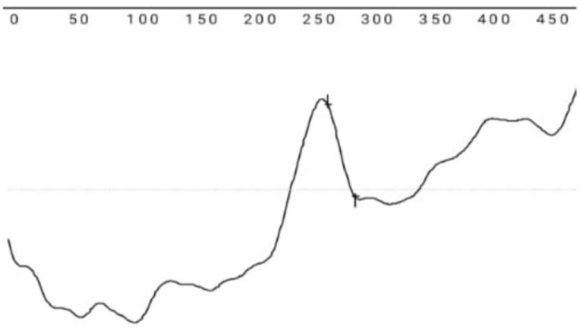

Fig. 1 Mean P300 waveform of age group 10–20 years

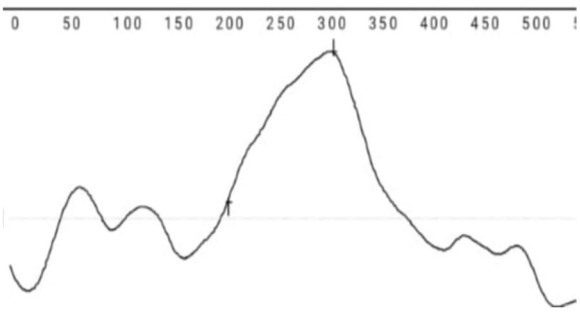

Fig. 2 Mean P300 waveform of age group 21–40 years

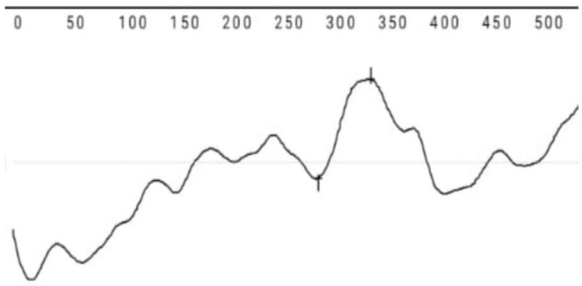

Fig. 3 Mean P300 waveform of age group 41–60 years

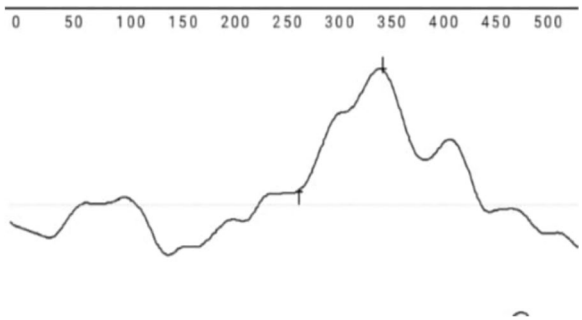

Fig. 4 Mean P300 waveform of age group 61–80 years

The latency and amplitude of P300 were assessed, and the impact of age on these measures was calculated separately for each group and subgroup using the Spearman rank correlation coefficient test. Key statistical parameters, including mean, standard deviation, and range of P300 amplitude and latency, are presented in Table 2.

These results are pivotal for elucidating the relationship between age and P300 measures, providing valuable insights into the impact of advancing age on cognitive processing, specifically in response to tone burst stimuli. The application of non-parametric tests ensures robust analyses despite potential deviations from normality in the dataset.

P300 in group 1

In group 1A (age range of 10–20 years), P300 amplitude ranges from 5.10 to 6.40 μv, and the latency was found between 253.00 and 267.34 ms (Fig. 1). In this age range, we found a strong positive correlation between age and amplitude of P300 ($r=0.96$, $p<0.001$), while no statistically significant correlation was found between latency and age. In group IB (age range:21–40 years), the amplitude was between 6.50 and 8.90 μv, and the latency was between 305.65 and 322.00 ms (Fig. 2). In this age group, a moderate negative correlation ($r=-0.43$, $p<0.05$) was found between age and amplitude of P300, while a strong positive correlation ($r=0.87$, $p<0.001$) was obtained between age and latency.

P300 in group 2

In group 2A (age: 41–60 years), P300 amplitude was found to be between 5.20 and 6.50 μv (Fig. 3). The P300 latency varies from 314.00 to 321.00 ms. Spearman rank correlation was calculated between age and P300 measures. It was found that amplitude has a strong negative

Table 3 Spearman rank correlation result of age and P300 measures in various groups

Age range	Amplitude	Latency
10–20 years	$r = .962^{**}$ $p = 0.000$	$r = .525$ $p = .080$
21–40 years	$r = -.433^{*}$ $p = 0.27$	$r = .876^{**}$ $p = 0.000$
41–60 years	$r = -.975^{**}$ $p = 0.000$	$r = .894^{**}$ $p = 0.000$
61–80 years	$r = -.936^{**}$ $p = 0.000$	$r = -.887^{**}$ $p = 0.000$
10–80 years	$r = -.749^{**}$ $p = 0.000$	$r = 0.914^{**}$ $p = 0.000$

*significance at 0.05 level

**Significance at 0.01 level

Table 4 Mann–Whitney *U* test result to evaluate the group-wise comparison of P300 measures

Age groups		Amplitude	Latency
10–20 years and 21–40 years	*Z*	4.88	4.88
	P	0.0001	0.0001
10–20 years and 41–60 years	*Z*	1.84	4.91
	P	0.06	0.001
10–20 years and 61–80 years	*Z*	4.80	4.85
	P	0.0001	0.0001
21–40 years and 41–60 years	*Z*	6.20	−3.98
	P	0.0001	0.0001
21–40 years and 61–80 years	*Z*	6.11	−6.14
	P	0.0001	0.0001
41–60 years and 61–80 years	*Z*	6.17	−6.18
	P	0.0001	0.0001

correlation ($r = -0.97$, $p < 0.001$) with age, while latency has a strong positive correlation ($r = 0.89$, $p < 0.001$).

In group 2B (age: 61–80 years), amplitude ranged between 2.70 and 4.60 μv and latency between 322.30 and 357.10 ms (Fig. 4). It was found that amplitude has a strong negative correlation ($r = -0.93$, $p < 0.001$) with age, while latency has a strong positive correlation ($r = 0.95$, $p < 0.001$). The Spearman rank correlation of both groups is given in Table 3.

Linear regression analysis was carried out to observe the change in amplitude and latency in different age ranges.

Comparison of P300 measures between groups

The Kruskal–Wallis test was used to check for any significant difference in P300 latency and amplitude across different age groups. There was a significant difference in P300 amplitude (*H*, 78.19; $p < 0.001$) and latency (*H*, 75.82, $p < 0.001$) between different age groups. Further, the Mann–Whitney *U* test was performed to make a pairwise comparison of age groups for latency and amplitude measures of P300. The results of the Mann–Whitney *U* test are shown in Table 4. From this table, it was observed that there is a statistically significant difference present in P300 latency between all the groups. In terms of amplitude, a significant difference was observed in all the age groups except groups 1A and 2A.

Discussion

The primary objective of this study was to examine the relationship between age and P300 measures, specifically amplitude and latency in the Indian population. The findings revealed a robust negative correlation between amplitude and age, signifying a decrease in P300 amplitude with advancing age. Additionally, a strong positive correlation was observed between latency and age, indicating an increase in P300 latency as individuals' age. These results align with previous studies by García de la Cadena et al., van Dinteren et al., Puttabasappa et al., Bourisly, Polich et al., and O'Connell RG [17–20, 22–24].

The division of the total age group into four distinct sub-groups facilitated a nuanced analysis of age-related effects. In the 10- to 20-year-old age group, a positive correlation between amplitude and age was noted, aligning with the findings of Bourisly AK [22]. This might be attributed to the neural maturation of the auditory cortex, which is reported to occur up to 10–12 years of age. The lack of statistically significant correlation for latency in this age group is consistent with existing literature. Significant differences in both amplitude and latency across different age groups were observed, highlighting a decline in cognitive abilities with age. The amplitude reduction in the 60- to 80-year-old age group compared to the 10–20-year-old age group underscores the age-related decrease in cognitive function. Regression analysis further demonstrated that amplitude increases at a rate of 0.95 μV/year and latency at 0.01 ms/year in the 10–20 years age range. In contrast, the 61–80 years age group exhibited a reduction in amplitude at a rate of 0.91 μV per year and an increase in latency at a rate of 0.65 ms/year. These findings contradict some previous studies, possibly due to the use of tone burst stimuli instead of speech stimuli.

The non-linear and inconsistent increase in P300 latency with age underscores the complexity of age-related cognitive changes. This study supports the hypothesis that cognitive abilities decline with increasing age. The insights gained contribute to our understanding of age-related variations in cognitive processing, specifically reflected in P300 measures. The protocols and tasks established in this study can be extended to explore individuals with various communication disorders

characterized by cognitive language decline. This expansion would enhance our understanding of how cognitive function, as reflected in P300 measures, is affected across diverse clinical populations.

Moreover, future studies could explore variations in P300 responses by employing different speech stimuli and investigating the impact of electrode position on the generation of P300. These refinements would contribute to a more comprehensive understanding of the nuances associated with cognitive processing and aging.

Conclusion

The P300 measurements undertaken in this study have offered valuable insights into the impact of aging on cognitive processing. The observed correlations between age and P300 amplitude and latency provide a clear depiction of the changes associated with advancing age. Consequently, P300 measures emerge as potential tools for investigating cognitive impairment linked to aging, opening avenues for future research in this domain.

In summary, the findings from this study not only shed light on the age-related changes in P300 measures but also lay the groundwork for further investigations that can deepen our understanding of cognitive functioning in both normal and pathological aging.

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Authors' contributions
AS is the corresponding author, prepared the study design, analyzed data, and did the statistical analysis. UG is involved in data collection and manuscript writing.

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We did not receive any funds for this study.

Availability of data and materials
The data sets used/analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Internal Ethical committee of the Maharashtra University of Health Science. Written consent was taken from adult participants and consent from parents was taken for participants below 16 years of age.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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