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Original Article

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Time Perception and Memory in Mild Cognitive Impairment and Alzheimer's Disease: A Preliminary Study

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Background and Purpose: Episodic memory is a system that receives and stores information about temporally dated episodes and their interrelations. Our study aimed to investigate the relevance of episodic memory to time perception, with a specific focus on simultaneity/order judgment.
Methods: Experiment 1 employed the simultaneity judgment task to discern differences in time perception between patients with mild cognitive impairment or dementia, and age-matched normals. A mathematical analysis capable of estimating subjects' time processing was utilized to identify the sensory and decisional components of temporal order and simultaneity judgment. Experiment 2 examined how differences in temporal perception relate to performance in temporal order memory, in which time delays play a critical role.
Results: The temporal decision windows for both temporal order and simultaneity judgments exhibited marginal differences between patients with episodic memory impairment, and their healthy counterparts ($p = 0.15$, $t(22) = 1.34$). These temporal decision windows may be linked to the temporal separation of events in episodic memory (Pearson's $\rho = -0.53$, $p = 0.05$).
Conclusions: Based on our findings, the frequency of visual events accumulated and encoded in the working memory system in the patients' and normal group appears to be approximately (5.7 and 11.2) Hz, respectively. According to the internal clock model, a lower frequency of event pulses tends to result in underestimation of event duration, which phenomenon might be linked to the observed time distortions in patients with dementia.

Keywords: Dementia; Time Perception; Memory, Episodic; Alzheimer Disease; Models, Statistical; Memory Disorders

INTRODUCTION

Tulving suggested that episodic memory is a system that receives and stores information pertaining to temporally dated episodes or events, along with spatio-temporal relationships among them.[1] According to Tulving, episodic memory encompasses "wh-" elements, such as

Author Contributions

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"when," "where," and "what." The "where" and "what" aspects are contingent upon stimuli from the external environment, the input of information to the corresponding sensory organs, and subsequent neural processing. However, time corresponding to 'when' does not emanate from a physical source, and we lack a sensory organ that is specifically dedicated to perceiving time. Nevertheless, we possess a vivid experiential perception of it.[2] Consequently, the perception of time is believed to be underpinned by specific internal neural processes that are aimed at achieving a coherent representation of the external world.

Considerable evidence indicates that the hippocampus plays a pivotal role in episodic memory in both humans,[3,4] and animals.[5,6] Analogous to the hippocampal place cells responsible for spatial representations of the external environment,[7,8] cells involved in temporal representations have been identified in the hippocampus of rodents and humans.[9-11] The function of these temporal cells in the hippocampus can be thought of as providing a specific mechanism for encoding temporal contextual information within episodic memory.

Alzheimer's disease (AD) is a progressive age-related neurodegenerative disease associated with distinct pathological changes that include extracellular accumulation of β-amyloid-containing plaques and intracellular development of tau-containing neurofibrillary tangles that primarily affect the medial temporal and cortical regions. Additionally, hippocampal atrophy represents a prominent feature of AD.[12] Cross-sectional studies employing magnetic resonance imaging (MRI) and histological analysis in AD have found decreased hippocampal volumes to be associated with β–amyloid,[13] and tau,[14] deposition. Clinically, AD is classically characterized by insidious and progressive episodic memory impairment.[15] In line with the significance of time perception in episodic memory, psychological time distortions were also observed in AD patients.[16,17] Much of the research on time distortion in AD has focused on duration estimation, employing various experimental methods, such as verbal reporting,[18] reproduction of elapsed time,[19] forced choice task with options like "long" and "short,"[20] and estimation of time intervals.[21] Aspects of psychological time also include simultaneity, successiveness, and temporal order. The duration of a stimulus is defined as the time elapsed between its onset and offset. Consequently, the estimation of duration hinges on the perceptual process of the onset and offset of the stimulus. Therefore, if the perception of the successiveness, temporal order, and simultaneity of events constitutes the first stage, judgment or estimation of duration can be regarded as the second stage.[2] However, studies on time perception in these aspects are rare in patients with episodic memory disorders.

Research on temporal processes, such as temporal order judgment and simultaneity judgment, has a longstanding tradition within psychophysics. The psychophysical methods widely used to study the temporal process are the binary simultaneity judgment (SJ2) task, and the binary temporal order judgment (TOJ) task, which consist of presenting two stimuli (A and B) with a temporal offset, temporal delay, or stimulus onset asynchrony (SOA) that varies across trials.[2] The ternary simultaneity judgment (SJ3) task blends SJ2 and TOJ tasks by allowing observers to report the three judgments: A first, A and B simultaneous, or B first.[22]

In our study, we aimed to investigate the relevance of episodic memory impairment to primitive time perception, such as simultaneity judgment and temporal order judgment. In Experiment 1, we used the SJ3 task to identify differences in time perception between patients with dementia and age-matched normals, while in Experiment 2, we examined how these differences relate to performance on temporal order memory in which the time delays play a critical role.[23]

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METHODS

Participants

We recruited 13 patients with dementia, and 13 age-matched normals. Two of the 13 patients complained of fatigue during the experiment, discontinued, and were excluded from further analysis. Therefore, the total number of patients was 11. The patient group was recruited based on the following criteria. Patients who were diagnosed with early AD or amnestic mild cognitive impairment (aMCI), with an Mini-Mental State Examination (MMSE) score of (10 to 26) points and a global deterioration scale (GDS) of 3 or more or clinical dementia rating (CDR) of 0.5 or more were selected as the patient group.[24,25] The diagnosis of aMCI was based on the following criteria, modified from Peterson's criteria[26]: 1) normal activities of daily living; 2) objective memory impairment on verbal or visual memory test, below the 16th percentile of age and education matched norms; and 3) not having dementia. Those with AD satisfied the core clinical criteria for probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association.[15] The age-matched normal group consisted of subjects with no neurological abnormalities, showing no abnormal MRI findings, with an MMSE score of ≥25, a CDR <0.5, and a GDS of ≤2.

Experiment 1

In Experiment 1, the SJ3 task was implemented. The experimental task involves reporting the temporal order or simultaneity of white circle stimuli presented on the left and right sides of a computer monitor (**Fig. 1**). Stimuli presented on the left and right are shown at different presentation times at various SOAs from −600 to +600 ms (left first to right first). Each SOA condition was −600, −300, −200, −100, −70, 0, +70, +100, +200, +300, and +600 ms. Considering that the subjects were elderly patients, the total number of trials was minimized by conducting three trials for each SOA to maintain the subjects' attention to perform the task. The 0 ms SOA is a condition in which left and right stimuli appear simultaneously. In the trial of each SOA condition, the subject decides whether the stimuli were "left first," "simultaneous," or "right first," and reports their decision using the arrow keys on the keyboard. The left key means "left first" judgment, the downward key means "simultaneous" judgment, and the right key means "right first" judgment. As soon as the patient reports his or her judgment by pressing the arrow key, the next trial begins.

Experiment 1 aims at a mathematical analysis that can estimate the subject's temporal processing mechanism. Based on the classical study of Sternberg and Knoll,[27] an observer model was constructed that explicitly represents the internal process of timing and decision

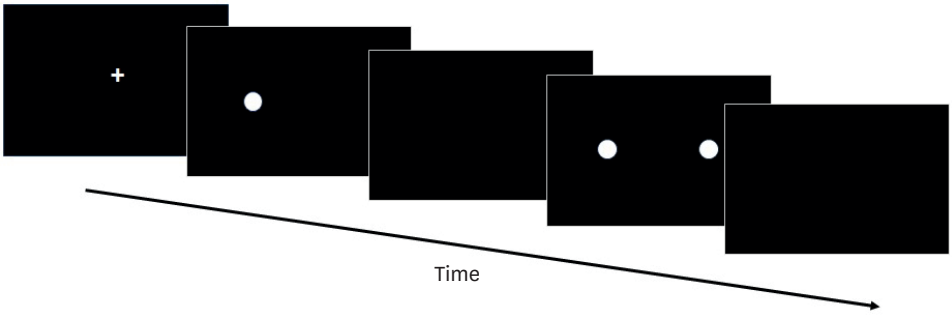

Fig. 1. Example of "left first" trial in SJ3 task. After 3 seconds of fixation, the first stimulus appears on the left or right side. Then, after an SOA of 0 to 600 ms, the second stimulus appears. The subject's task was to report within 5 seconds whether the stimuli appeared left first, both at the same time, or right first.

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making for temporal order and simultaneity judgment.[2,28] The temporal processing model proposed in García-Pérez and Alcalá-Quintana[2] assumes that judgment of temporal order and simultaneity consists of sensory, decisional, and response components. The sensory component describes the process by which stimuli arrive at the central decision system with a neural delay. The signal of the stimulus arriving at the central decision system has a distribution with a mean and standard deviation, due to neural noise. In this study, simple exponential distribution $g(t)$ was assumed as this distribution whose mean was $1/\lambda+\tau$, and whose standard deviation was $1/\lambda$ (Eq. 1):

$$g(t)=\lambda\exp[-\lambda(t-\tau)],\ t\geq\tau \quad (1)$$

Given the parameter τ of difference in arrival time of the signals from right and left stimulus ($\tau=\tau_R-\tau_L$) and the parameters λ_L and λ_R that determine the mean arrival times, the probability distribution of arrival-time difference (d) with the SOA (Δt) in the central decision system has the following asymmetric Laplace distribution (Eq. 2):

$$f(d\ ;\ \Delta t)=\begin{cases}\dfrac{\lambda_R\lambda_L}{\lambda_R+\lambda_L}\ exp[\lambda_L(d-\ \Delta t-\ \tau)]\\ \dfrac{\lambda_R\lambda_L}{\lambda_R+\lambda_L}\ exp[\lambda_R(d-\ \Delta t-\ \tau)]\end{cases} \quad (2)$$

The subject's judgment of temporal order and simultaneity does not depend solely on the processing time of the stimuli, i.e., when they are presented with a very small SOA, the tendency to judge stimuli as simultaneous increases. This aspect provides a basis for assuming that the central decision system has a temporal resolution or decision window. Given the difference in arrival time of two signals in a given SOA (Δt) condition, the probability of left first, simultaneous judgment, or right first depends on the temporal decision window of the simultaneous judgment. As a result, when the range of temporal decision window is parameterized by delta (δ), distribution of left first (ψ_L), simultaneous (ψ_S), and right first (ψ_R) judgments are as follow:

$$\psi_L(\Delta t)=\int_{-\infty}^{-\delta}f(z;\ \Delta t)dz=F(-\delta;\ \Delta t)\ \ (3a)$$

$$\psi_R(\Delta t)=\int_{\delta}^{\infty}f(z;\ \Delta t)dz=1-F(\delta;\ \Delta t)\ \ (3b)$$

$$\psi_S(\Delta t)=\int_{-\delta}^{\delta}f(z;\ \Delta t)dz=F(\delta;\ \Delta t)-F(-\delta;\ \Delta t)\ (3c)$$

The parameters of the above model were estimated using the MATLAB (http://www.mathworks.com) source code published in the Alcalá-Quintana and García-Pérez's study.[28] In our study, we estimated the parameters λ and τ, which correspond to the sensory component of temporal order and simultaneity judgment, respectively, and the parameter δ, which corresponds to the decisional component, for each subject. We then evaluated whether these parameters were statistically different in the normal and patient groups.

Experiment 2

In Experiment 2, subjects performed the temporal order memory (TOM) task from Tolentino's 2012 study,[23] to see how the timing processes identified in Experiment 1 relate to episodic

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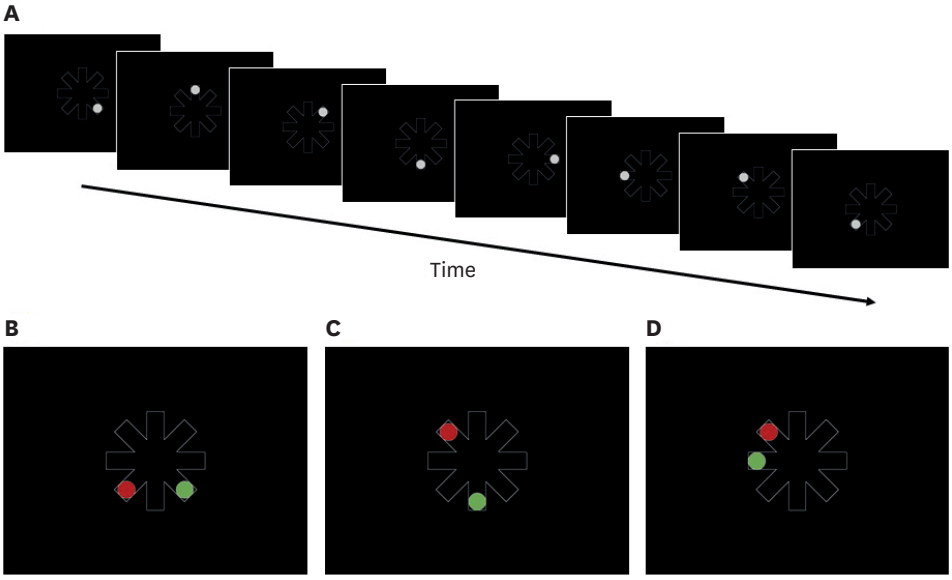

Fig. 2. Example of temporal order memory task. (A) An example of a stimulus sequence in the encoding phase. To eliminate afterimage effects, the display was masked for 1 second by a gray mask (not shown). (B-D) Exemplar test screens in retrieval phase. In (B-D), the screen represents 6, 2, and 0-lag separation, respectively.

memory. Each trial in Experiment 2 consisted of an encoding phase, followed by a retrieval phase. In the encoding phase, a white circle (3-cm diameter) appeared at the end of a randomly selected arm for 2 seconds. The display was masked for 2 seconds by a gray mask to eliminate afterimage effects. Another circle then appeared at the end of a different randomly selected arm for 2 seconds. This continued, until a circle had been presented once at the end of each of the 8 arms in a random sequence that varied on each trial. On the retrieval phase, subjects were simultaneously presented with two circles, one red and one green, for 5 seconds. The location of each circle was the 2 positions of the sequence in the encoding phase. Then, the participant was asked to indicate which circle appeared earlier in the sequence. Temporal separations of 0, 2, 4, and 6 lags were randomly selected for each retrieval phase. Each lag represented the number of circles that occurred during the encoding-phase sequence between the 2 circles simultaneously presented during the retrieval phase. For example, a 6-lag separation in the retrieval phase would consist of 2 circles that occurred with six circles between them during the encoding-phase sequence (**Fig. 2**). Previous study has reported that as temporal separation delay increases, interference is likely to be reduced, leading to better temporal order memory, and this relationship is linear.[23] In our study, we estimated the relationship between separation delay and temporal order memory as a linear model, and considered the slope of the linear model as the degree to which the temporal pattern separation claimed by the authors of the previous study was for each subject. We statistically verified whether this slope differed for each subject group, and what relationship it had with the parameters identified in Experiment 1.

RESULTS

In Experiment 1, the SJ3 task was performed in the normal group and the patient group, and the internal process of temporal order and simultaneity judgment was modeled. **Fig. 3** depicts the average probability "left," "simultaneous," and "right" response of the normal group and

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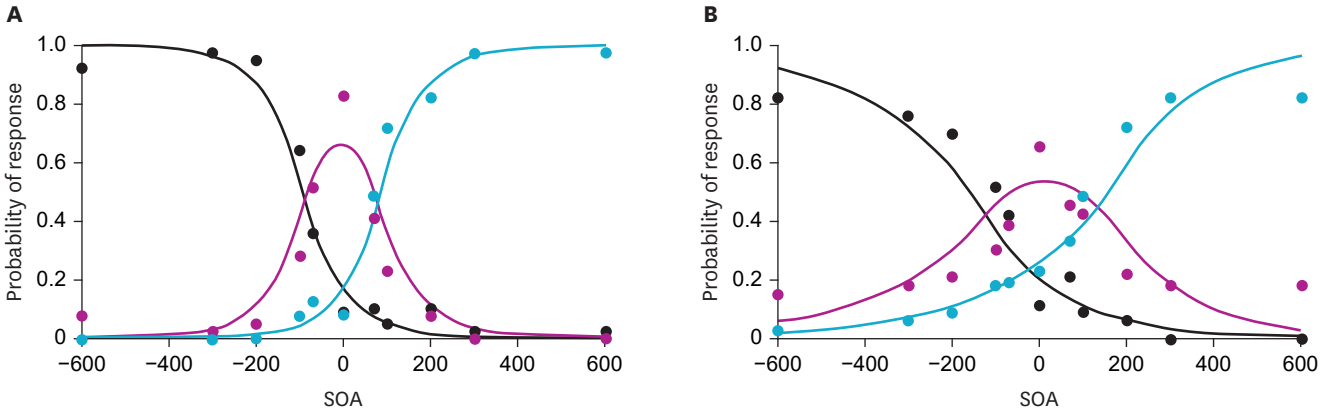

Fig. 3. Averaged response probability and fitted model-based psychometric function of the (A) normal, and (B) patient groups. The black, red, and blue dots represent the "left first", "simultaneous", and "right first" response, respectively. In Eq. (3), the black line represents ψ_L, the red line represents ψ_S, and the blue line represents ψ_R.
SOA: stimulus onset asynchrony.

the patient group, and the model-based psychometric function. Qualitatively evaluated, it can be speculated that the temporal decision window for simultaneity is wider in the patient group than in the normal group. To confirm this conjecture, it was verified whether the $1/\lambda_L$ and $1/\lambda_R$, corresponding to the estimated standard deviation of arrival time of left and right stimulus signals from each subject, τ corresponding to the difference in arrival time, and δ corresponding to the range of the temporal decision window, were statistically different in the normal group and the patient group (**Fig. 4**). The results showed that none of these parameters were statistically different between the normal and patient groups; however, a slight, albeit not statistically significant, difference in δ was suspected (p=0.15, t[22]=1.34).

The TOM task in Experiment 2 examined how temporal separations of 0, 2, 4, and 6 lags in the encoding phase affected the recall of temporal order in the retrieval phase of normal and patient groups. A 2-way analysis of variance with lag and group as factors revealed that only the main effect of lag was significant, (F[3]=3.06, p<0.05), while the group effect and the interaction between group and lag were not statistically significant (**Fig. 5A**). The relationship between each subject's temporal separation delay and their recall of temporal order was estimated by the slope of a first-order linear model, and tested for group differences (**Fig. 5B**). The results showed a marginal difference between the normal and patient groups, but did not reach statistical significance (p=0.08, t[22]=1.82).

The correlation between the parameters of each subject's model-based psychometric function in the SJ3 task and the linear model slope for TOM task performance was verified to identify the relationship between the internal processing of temporal order/simultaneity judgment and temporary pattern separation in episodic memory (**Fig. 6**). As a result, the marginal negative correlation between the decision temporal window (δ) and the temporary pattern separation could only be seen in the normal group (Pearson's ρ=−0.53, p=0.05).

DISCUSSION

In the present study, we aimed to investigate how the perception of temporal order and simultaneity affects episodic memory. The internal process of timing judgment was probed through psychophysical experiments and estimation of the model-based psychometric

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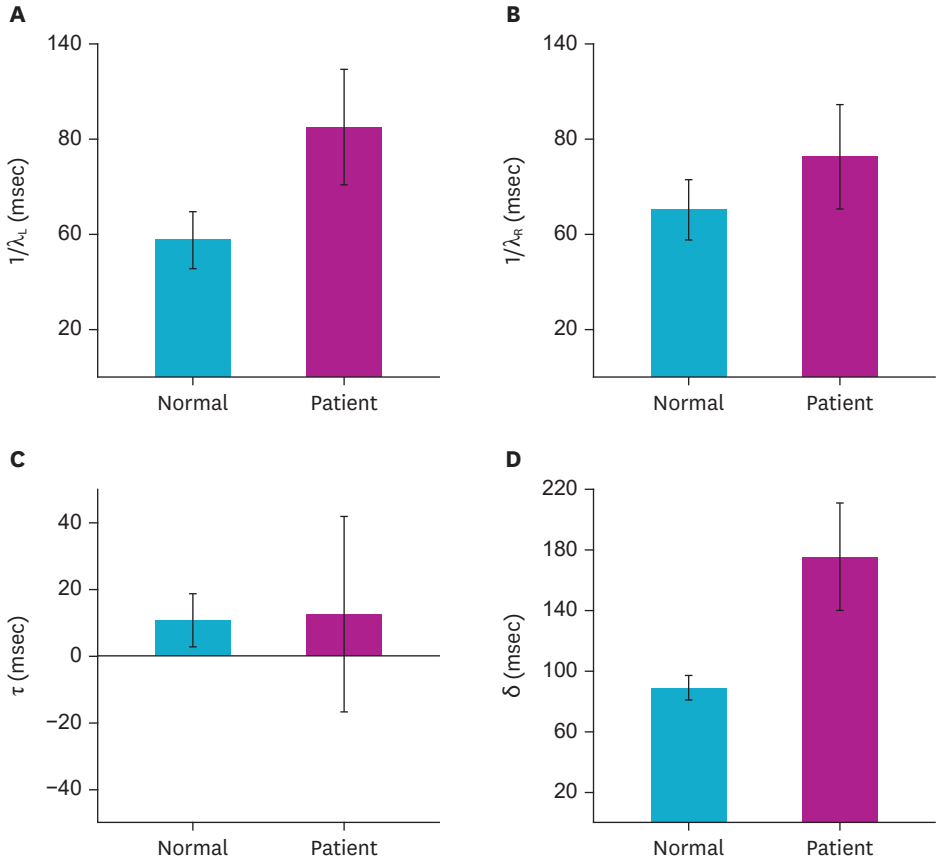

Fig. 4. Averaged estimated parameters of model-based psychometric function. Error bar represents the standard error of mean. Light gray and deep gray depict normal and patient group, while (A and B) represent the estimated standard deviation of the arrival times of the left ($1/\lambda_L$) and right ($1/\lambda_R$) stimulus signals, respectively; (C) represents the estimated difference in arrival times, τ; and (D) represents the decision time window, δ.

function. We found that the decision window for temporal order and simultaneity judgments may be broader in patients with episodic memory impairment, than in healthy individuals, although this finding did not reach statistical significance. We also found that this temporal decision window may be related to the temporal separation of the content in episodic memory.

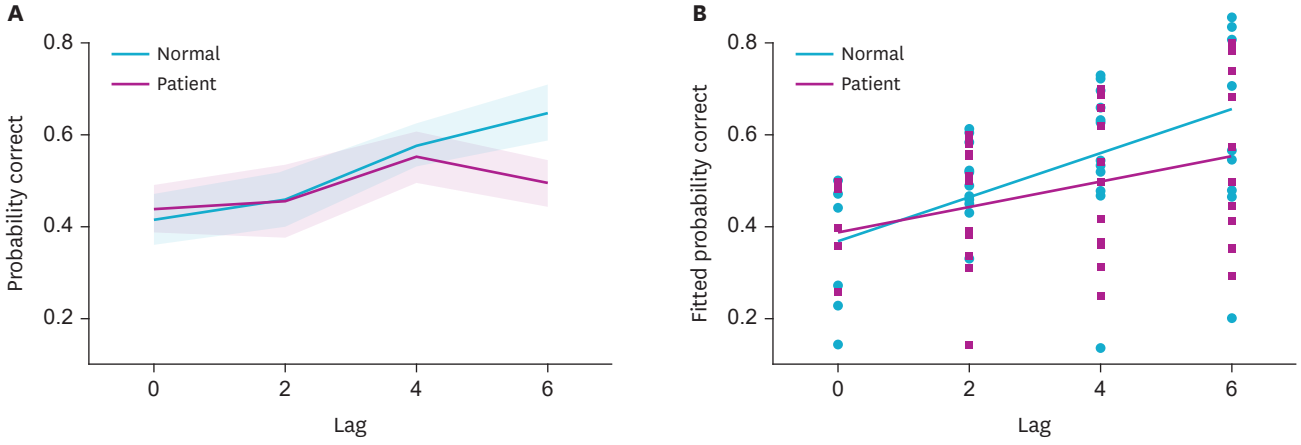

Fig. 5. Probability correct of the (A) temporal order memory task, and (B) fitted linear function. The shaded area represents standard error of mean.

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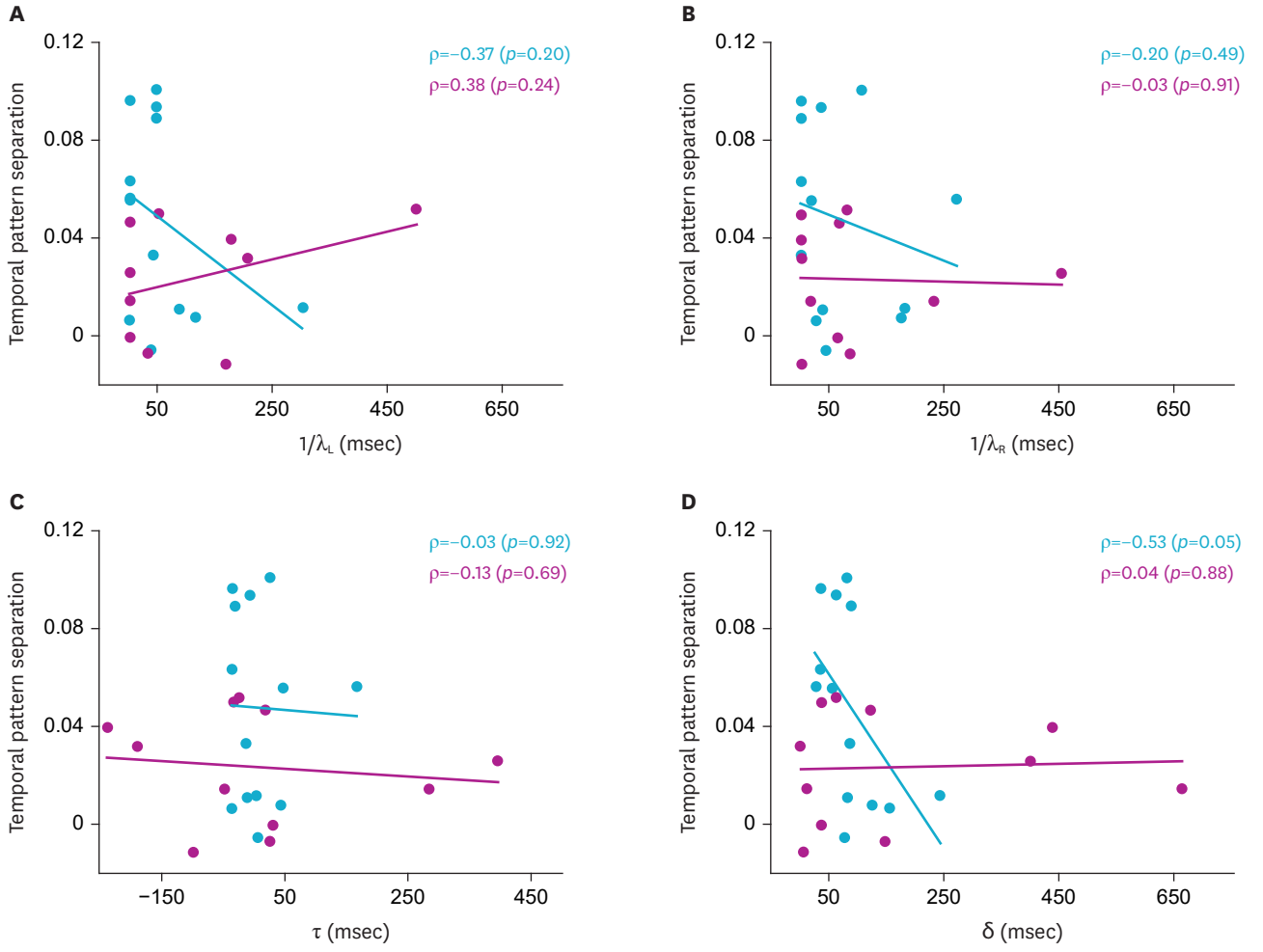

Fig. 6. Correlation between the temporal pattern separation in the TOM task and the estimated parameters, (A) $1/\lambda_L$, (B) $1/\lambda_R$, (C) τ, and (D) δ in SJ3 task of the normal (blue) and patient (red) groups.
TOM: temporal order memory.

A long-standing and influential theory of psychological time is the internal clock model,[29-31] which assumes an internal clock consisting of a pacemaker emitting pulses, and an accumulator (or counter) collecting these pulses. Attention is believed to play a pivotal role in gating these pulses to the accumulator. Within this model, the pulses currently accumulated in working memory are compared with a previously stored value in reference memory, representing the duration of the event to be remembered.[30] Event pulses emitted by the pacemaker possess a certain temporal resolution, a property typically attributed to the sensory system.[32] However, in the case of temporal judgment, this resolution is thought to include a higher-level component, such as a decisional time window. This is because, while the precise resolution can vary depending on sensory modality, it generally spans from tens to hundreds of milliseconds. In our study, the estimated decision window for event order and simultaneity judgments, denoted as δ, averaged 89 and 175 ms in the normal group and the patient group, respectively. Consequently, based on our findings, the frequency of visual events accumulated and encoded in the working memory system appears to be approximately 5.7 and 11.2 Hz in the patients' group and the normal group, respectively. According to internal clock theory, the duration of an event is estimated based on the amount of information accumulated; thus, a lower frequency of event pulses tends to result in

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underestimation of event duration. This phenomenon is believed to be linked to the observed time distortions in patients with dementia.[17]

The main limitation of this study is that when comparing the normal and patient groups, the probability of response and correctness, and the estimated parameters of the psychometric function in Experiments 1 and 2, did not attain statistical significance. Generally, a substantial number of trials is required to accurately estimate the psychometric function based on probabilities of response or correctness. However, since the experiment in this study was conducted on elderly patients, there were many restrictions on the number of trials and the duration of the experiments. It is also worth noting that it is dangerous to categorically conclude research results according to p value.[33] Consequently, we are planning further research efforts to address the limitations identified in this study.

Given the importance of time in episodic memory, it is important that attempts are made to integrate traditional psychophysical studies of time with neuropsychological studies of memory disorders. We trust that the present study will provide motivation for such research.

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