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Research article

The feasibility and practicality of auxiliary detection of spatial navigation impairment in patients with mild cognitive impairment due to Alzheimer's disease by using virtual reality

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ABSTRACT

Background: Spatial disorientation in patients with mild cognitive impairment due to Alzheimer's disease (MCI due to AD) has become a subject of great interest. Medical practitioners are concerned about the serious issue of these patients who are getting lost. Therefore, the early detection of MCI due to AD is crucial.
New methods: We designed virtual reality (VR) protocols to test spatial recognition abilities. Our devices mainly included the Vive Pro Eye and the Steam VR program. We tested the three groups: young cognitively unimpaired (YCU), older cognitively unimpaired (OCU) and MCI due to AD. We also administered the Cognitive Abilities Screening Instrument and the Questionnaire on Everyday Navigational Ability for comparison.
Results: We adopted the testing results of 2 YCU, 3 OCU, and 4 MCI due to AD for analysis. Concerning cognitive abilities, YCU and OCU had better performance than MCI due to AD respectively. It was consistent with the recent memory and the total scores of the Cognitive Abilities Screening Instrument.
Comparison with existing methods: We introduced a real-life setting, the Tzu-Chiang campus at National Cheng Kung University, into the VR environment. It allowed us to assess daily road-recognizing abilities of participants in a controlled testing environment.
Conclusions: Several limitations were considered in this study, such as limited number of participants and low-quality images on the screen. Nonetheless, this device has the potential to serve as a screening tool for MCI due to AD based on its feasibility and practicality.

1. Introduction

Space recognition has been one of the greatest interests to humankind. In 1948, Tolman, a behavioral neuroscientist, introduced the concept of a cognitive map and suggested that the brain could create map-like representation [1]. In 1971, O'Keefe and Dostrovsky discovered a special cell population in the hippocampus called place cells. In 2005, the Mosers identified grid cells in the entorhinal

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cortex, which were involved in the construction of spatial models [2,3]. Since then, human researches on space representations of the brain have developed by leaps and bounds.

Human spatial navigation involves self-motion cues, landmark recognition, and egocentric-allocentric navigation patterns. Egocentric representation is mainly based on the first-person viewpoint in exploring the environment, which is often related to the function of the parietal lobe; while allocentric navigation, a hippocampal-related function, is based on third-person viewpoint [4,5]. Some studies pointed out that grid cells were correlated with integration of spatial information through path integration. The cognitive map formation, cooperating with human senses of location (SoL) and other abilities, finally affects human navigation behaviors [6].

Many people living with Alzheimer's disease (AD) suffered from spatial navigation impairment due to lesions in the brain. Early AD patients have progressive brain atrophy in the medial temporal lobe, especially in hippocampus and entorhinal cortex [7,8]. Therefore, AD patients sustain gradual declination in spatial recognition and memory, which contributes to substantial impact on daily life.

AD patients are at considerably high risk of getting lost (GL). SoL impairment usually occurs before GL because they adopt alternative strategies, such as landmark referencing [6,9,10]. Grid cells were a better observational indicator for allocentric navigation strategies [11], and some studies had also shown that the entorhinal cortex also responded to egocentric direction [12]. Therefore, we hope to find a method regarding navigation abilities related to the entorhinal cortex to explore the relationship between early AD and spatial navigation impairment.

Researchers mainly used one of the two research methods for road recognition in the past. The first is the real world (RW) test, which observes explorational behavior of participants in actual spaces, but it is easily limited by environmental conditions. In addition, different researchers conducted their studies in different locations and those studies cannot be reliably replicated by other scientists. An alternative approach is virtual reality (VR) tests, which could be done by tablets, computer screens, or immersive headsets [5]. It has multiple advantages, especially the safety during tests. VR devices have even been used to explore chimpanzees' navigation and foraging behavior nowadays [13]. The main disadvantage of testing in VR, however, is that the navigation behavior in the virtual space was not as same as in the RW. Dizziness or vertigo occurred in subjects might also affect the results of the experiments.

Therefore, this study devoted to figure out whether it was possible to use computer software that turned RW scenes into VR. We aimed to introduce a safer and a more standardized test for navigation abilities, and we anticipated that our method would be able to assist medical workers in getting more acquainted with human navigating behavior of mild cognitive impairment (MCI) due to AD patients. The aims of this study were as follows. The first objective was to assess **feasibility**. We designed a VR spatial navigation task to acquire complete data from participants and to distinguish the navigational differences between individuals with normal cognition and those with MCI due to AD. The second was **practicality**. We converted RW scenes into VR, and we hoped that the combination of the advantages of the two methods may increase the applicability of the VR apparatus for daily navigation testing.

2. Methods

2.1. Description of VR apparatus and space model construction

Based on previous research [6], we took the Tzu-Chiang campus in National Cheng Kung University (NCKU) as our spatial model because of its straight roads and square and clear building arrangement patterns. This research mainly used immersive VR, which included Vive Pro Eye head-mounted display (HMD), joysticks (or handles), and sensors. These devices were contract-manufactured by HTC International Corporation (**See** Appendices Fig. 1.). All of the devices were controlled by the software, Steam VR, and Unity game

Fig. 1. *The beginning of the formal test.* The picture shows a map, on the left-hand side in the virtual space, and the blue light beam on the right for functional manipulation. The map clearly demonstrated 5 spots, A, C, E + D, B, and the light blue spot represented the starting point. Participants could read literal instructions on a billboard, and, at the same time, the recording repeated the words from earphones on the head-mounted display. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

engine. After the subjects were instructed and finished wearing the HMD, the virtual-space-displaying screen started playing virtual scenes in front of them. The subjects held two functionally-different joysticks in both hands respectively: a virtual space map was displayed above the left joystick in their views, and the right joystick was for movement manipulation (Fig. 1.). They did not actually walk. Subjects were expected to punch in by their right thumb, and to move forward or to make selections by the forefinger. When subjects started answering questions, the blue light beam emerged on the screen. Subjects should move their right arm to make the blue light beam point at the option bars, then the option bars turned orange. Subjects should press the right-forefinger button on the joystick within 1.5 s for answer entering.

As for space model settings, we selected five points that each point was not visible from other points due to blockage of buildings (Fig. 1.). The starting point was the Chi-Mei Building of NCKU. It was selected for its white exterior that was distinct from other brick-red buildings. Subjects were required to complete tests one lap each in a counterclockwise/clockwise order to reduce bias caused by traveling in different directions [6]. At the same time, subjects needed to complete punch-ins in the assigned spots. The first lap consisted of three spots A, C and E, and the second comprised D and B. Virtual time of the test was set at 9:00 in the morning, and the weather was sunny, in order to decrease visual interference during tests. In order to make the VR space model resemble a RW scene, we added clouds, lawns, trees, street lights, cars and other elements in the virtual test space. The appearance and materials of the floor and buildings also strived to be as similar as the real situation (**See** Appendices Fig. 2.). We named the whole settings of the device as Pai-Jan Virtual Reality, abbreviated PJVR.

2.2. Descriptions of VR testing classroom

Most participants finished their experiment in the VR classroom of College of Medicine, NCKU. The area of the VR classroom was 8.2 m × 7 m, with the height ranging from 2.2 to 3.5 m. The setup included one set of computer devices, a 75-inch television, one desk, chairs, and four sensors. Cognitive Abilities Screening Instrument (CASI) [14], the Questionnaire on Everyday Navigational Ability (QuENA) [15] and other non-VR events were conducted on the desk. As for VR testing, the researchers initiated, controlled and monitored the systems installed on the computer, while the participants stood in the center of the classroom with the HMD and joysticks to complete the experiments (**See** Appendices Fig. 3.). The television provided a broader view of the virtual space that the participants were in, and it allowed the researchers to easily know the current situations of the participants and to give immediate assistance when needed.

2.3. Subjects

We recruited 4 young cognitively unimpaired (YCU), 3 older cognitively unimpaired (OCU), and 9 MCI due to AD Taiwanese participants. YCU ranged from 20 to 40 years old; OCU and MCI due to AD were from 55 to 80 years old. The inclusion criteria are mentioned below: Clinical Dementia Rating (CDR) Scale [16] of YCU and OCU was 0; MCI due to AD was 0.5. No other physical or mental diseases were a must. The exclusion criteria of this study included the following six points. First, the people who were illiterate, or those who barely used characters in their daily life. Second, the subjects had obvious language problems and cannot understand verbal guides. Third, those who had a high-activity rate in or nearby the campus of NCKU (especially Tzu-Chiang campus) for avoiding our subjects from being familiar with the environment. Fourth, the basic sensory organs and vestibular system of subjects were abnormal. Fifth, subjects had obvious visual and hearing problems. Sixth, subjects had other mental symptoms, such as depression, which might affect cognitive function during the tests. The OCU and MCI due to AD subjects were all recruited from the Memory Clinic, National Cheng Kung University Hospital. The YCU participants were volunteers invited by the researchers. The study was reviewed and approved by National Cheng Kung University Hospital Institutional Review Board for the Protection of Human Subjects [ID: B-BR-110-046]. All ethical regulations were fully stuck to and executed by all the members in this research team. After explaining the procedures of the experiment, risks, conflicts of interest and other matters in detail, subjects signed informed consent. The subjects participating in this study were all with clear consciousness.

2.4. Research process

This study consisted of two parts: we conducted QuENA [15] and CASI [14] first; we then completed the PJVR test. All research took place in the VR classroom of College of Medicine, NCKU, or in the conference room of Institute of Gerontology. We pursued the completeness of the tests in every case; therefore, the testing time took about 2–4 h, including 1 h in total for the QuENA and CASI. However, if the subject had taken CASI within half a year, the former data would be used and no additional one would be administered.

We designed a four-step PJVR road-recognizing test. First, we put forth detailed instructions to participants. Second, the researchers in person demonstrated the practice mode once (**See** Appendices Fig. 4.). Third, subjects entered the practice mode until they could almost operate the devices on their own. However, considering potential fatigue and comprehension problems of every participant, we recommended at most two-time practice-mode practicing being adequate. Fourth, subjects initiated the formal test. In the formal test, participants must complete the whole set of questions and requests at each punch-in point. These questions included punch-in location, distance, time as well as direction judgments (**See** Appendices Fig. 5–7.). After the subjects completed a total of five punch-in points and related questions in a two-lap test, the experiment declared finished. During the process, if the subject expressed a sense of dizziness or vertigo, the experiment was suspended and later continued as soon as the situation was relieved.

The terms of PJVR test in this study are defined as follows. Angle deviation (*Ang*) is the angle between pointing-to-the-start direction pointed by subjects and the correct direction. The subject is undoubtedly the center of the angle. Time deviation (*Tim*) represents the difference between subjectively-recognizing and actual elapsed time from the starting point to the punching point. Note that if any events unrelated to the test process occurred during the tests, such as resting time due to dizziness or vertigo, the time would be deducted in the final analysis. Distance deviation (*Dis*) is the difference of subjectively-judged distance and real distance between two consecutive points. Linear deviation (*Lin*) is a relative value based on the coordinates established in the system determining the degree of difference between the location where the subject punched in and the correct punching point. In the following section, *Ang* point X would be denoted as *Ang*X. X could be any points (A, B, C, D, E) in this research. The naming follows the same rules in other categories.

2.5. Data collection and analysis

All data was properly stored in an ethical manner. The data of this study were analyzed by using SPSS (version 17.0). All continuous variables, including age, years of education, QuENA score, CASI score, and VR data were analyzed by ANOVA, and the LSD test was used for the post-hoc test. *P*-values <.05 were considered significant.

Table 1
Demographic data, neuropsychological tests and PJVR test results.

Variables	YCU ($n = 2$)	OCU ($n = 3$)	MCI due to AD ($n = 4$)	p-value	Post hoc (*LSD*)
Sex (M:F)	1:1	2:1	2:2	–	
Age (years)	21.50 (2.12)	69.00 (4.36)	66.75 (9.88)	0.001***	a, b
Education (years)	14.50 (2.12)	15.67 (0.58)	14.50 (1.91)	0.627	
CDR	0.00 (0.00)	0.00 (0.00)	0.50 (0.00)	–	
CASI total score	96.75 (1.77)	94.33 (0.76)	82.38 (5.94)	0.011*	d, e
Remote memory	10.00 (0.00)	10.00 (0.00)	10.00 (0.00)	–	
Recent memory	11.75 (0.35)	10.00 (0.50)	2.88 (2.10)	0.001***	d, e
Attention	8.00 (0.00)	8.00 (0.00)	7.50 (0.58)	0.266	
Mental manipulation^{L}	9.00 (1.41)	10.00 (0.00)	9.50 (1.00)	0.519	
Orientation	18.00 (0.00)	18.00 (0.00)	14.25 (2.50)	0.053	
Abstract thinking	10.00 (0.00)	9.33 (1.53)	10.00 (1.41)	0.787	
Language	10.00 (0.00)	10.00 (0.00)	10.00 (0.00)	–	
Drawing	10.00 (0.00)	9.67 (0.58)	9.75 (0.50)	0.755	
Animals^{L}	10.00 (0.00)	9.33 (1.15)	8.75 (1.50)	0.541	
QuENA total score	3.50 (2.12)	1.67 (2.89)	3.75 (2.63)	0.589	
LSA	1.00 (1.41)	0.33 (0.58)	0.75 (0.96)	0.736	
ED	1.00 (1.41)	0.33 (0.58)	1.25 (0.96)	0.486	
INA	1.00 (1.41)	0.67 (1.15)	1.50 (1.00)	0.642	
HD	0.50 (0.71)	0.33 (0.58)	0.25 (0.50)	0.880	
***Ang* (°)**					
A^{L}	16.17 (9.89)	13.33 (10.84)	134.76 (138.05)	0.264	
C	8.39 (1.79)	2.98 (1.90)	35.58 (22.81)	0.079	
E	2.60 (0.23)	14.96 (13.07)	50.02 (68.66)	0.502	
D	14.74 (2.11)	44.41 (25.55)	106.82 (75.42)	0.195	
B	26.37 (5.75)	45.98 (32.08)	36.90 (23.60)	0.705	
***Tim* (minutes)**					
A	0.27 (0.34)	1.75 (1.34)	7.13 (5.48)	0.152	
C^{L}	1.62 (1.57)	4.91 (5.14)	8.33 (6.46)	0.409	
E	0.47 (0.63)	3.32 (2.01)	6.84 (6.09)	0.305	
D^{L}	0.55 (0.62)	5.31 (8.08)	3.50 (2.38)	0.602	
B	1.33 (1.53)	2.83 (2.77)	4.13 (1.79)	0.369	
***Dis* (meters)**					
A	164.27 (60.81)	83.54 (45.39)	597.98 (831.61)	0.510	
C	242.66 (82.07)	224.23 (88.94)	237.32 (155.52)	0.985	
E	201.85 (127.22)	224.48 (115.99)	414.37 (196.47)	0.265	
D	46.55 (4.23)	99.78 (49.75)	146.85 (93.99)	0.336	
B^{L}	42.61 (0.95)	278.35 (149.65)	270.96 (183.62)	0.257	
Lin					
A	7.17 (3.59)	7.08 (1.80)	88.79 (78.49)	0.171	
C^{L}	9.56 (9.23)	20.59 (6.45)	205.14 (58.86)	0.002**	b, c
E	14.99 (5.66)	19.70 (16.86)	83.61 (78.58)	0.294	
D	5.93 (0.56)	12.17 (1.97)	38.65 (59.39)	0.608	
B	6.93 (7.35)	12.75 (4.36)	67.13 (34.89)	0.040*	b, c

(Note: Data are presented in the table as mean (standard deviation). Abbreviations: YCU, Young Cognitively Unimpaired; OCU, Older Cognitively Unimpaired; MCI due to AD, mild cognitive impairment due to Alzheimer's disease; MMSE, Mini-Mental State Examination; CASI, Cognitive Abilities Screening Instrument; CDR, Clinical Dementia Rating; QuENA, Questionnaire on Everyday Navigational Ability; LSA, Landmark and Scene Agnosia; ED, Egocentric Disorientation; INA, Inattention; HD, Heading Disorientation; Ang, Angle Deviation; Tim, Time Deviation; Dis, Distance Deviation; Lin, Linear Deviation.
*$p \leqq 0.05$; **$p \leqq 0.01$; ***$p \leqq 0.001$. Post hoc: a, YCU < OCU; b, YCU < MCI due to AD; c, OCU < MCI due to AD; d, YCU > MCI due to AD; e, OCU > MCI due to AD. L means Levene's test of homogeneity is significant.).

The main purpose of this study was not concentrating on over-/under-estimation judgments of time and distance, so the deviations in this statistical analysis were processed in absolute values.

3. Results

We set complete testing data of 2 YCU, 3 OCU, and 4 MCI due to AD participants into final analysis. The statistical results were shown in Table 1.

3.1. Analysis of demographic variables

No age differences were between OCU and MCI due to AD groups. Concerning educational years, no significant differences were observed among the three groups. It was worth mentioning that the educational years of our subjects were relatively high. All of the participants who got into the final analysis had finished a 12-year-long compulsory education in Taiwan.

3.2. Analysis of questionnaire scores

We found YCU and OCU, respectively, having higher scores than MCI due to AD in total and recent memory scores of CASI. CASI reflected the problem of recent memory in MCI due to AD participants. QuENA did not show any differences among groups.

3.3. Analysis of PJVR testing data

In *Ang*, we found out that OCU had better performances in point A and C, while YCU performed better in point E, D and B. Concerning *Lin*, OCU had better grades in point A, but YCU had better performances in the remaining points. *Lin*C and *Lin*B were the only two categories indicating differences between MCI due to AD and other groups, respectively. Furthermore, we also found that MCI due to AD participants got lost in the VR test more frequently, so they had higher standard deviation than other groups. Several categories or points did not pass Levene's test of homogeneity. This might be due to our small number of participants.

No significant differences were found in *Tim* and *Dis*. While answering the questions regarding *Tim*, participants might have difficulty remembering how long they had been through the test. In addition, every individual had a different concept of time. Considering *Dis*, many participants ($n = 12$) reported that no comparable standard or scales were displayed in distance judgment. They mostly guessed the distance by comparing the length between two points on the map.

3.4. Feedback from participants and dropout reasons

Two YCU data were excluded because of the different testing room in the conference room of Institute of Gerontology and walking speed abnormalities in the virtual space due to systematic errors (Table 2). Three MCI due to AD participants were unable to complete the test mainly due to cybersickness. The other two participants had difficulties manipulating joysticks and navigating, which might stem from low comprehension of using VR devices and inflexible arm movement. These situations contributed to their impatience, and the participants finally withdrew from the experiment. Noted that no standardized exit or feedback questionnaire was carried out. The participants were free to give any feedback, suggestions or complaints, and the researchers documented these comments for future improvements.

4. Discussion

This study integrated RW scene into a VR space for **practicality**. PJVR offered several advantages. We might assess spatial navigation impairment of MCI due to AD patients during their daily lives and predict the environmental conditions under which patients might get lost. This device also provided a promising idea of incorporating various RW scenes, including neighbor areas or communities, into VR [17]. However, we observed that the distance was often underestimated in the VR scene, similar to findings in previous

Table 2
Feedback from participants and dropout reasons.

Variables	YCU	OCU	MCI due to AD
Total participants	4	3	9
Analysis adopted	2	3	4
Total dropouts	2	0	5
Due to cybersickness	0	0	3
Due to impatience or fatigue	0	0	2
Due to systematic errors	2	0	0
Cybersickness during tests	0	1	6
Percentage of dropouts due to cybersickness	0 %	0 %	50 %

Abbreviations: YCU, Young Cognitively Unimpaired; OCU, Older Cognitively Unimpaired; MCI due to AD, mild cognitive impairment due to Alzheimer's disease.

studies [18]. This discrepancy implied that the representation of RW scenes in VR was not entirely faithful. This might be attributed to current technological constraints that were not able to present high quality images in HMDs.

In contrast to our previous study [6], we observed differences among groups in *Lin*B and *Lin*C. Although this could partly arise from our small size of participants, different ways of presenting the VR and RW scenes could be in charge of the results. Nevertheless, both methods showed spatial navigation differences among groups. They could mutually serve as complementary approaches for future studies. However, when it comes to improvements over our previous RW study, this VR research successfully resolved traffic and environmental problems. In the RW tests, cars and pedestrians might affect the testing results that participants might get anxious to avoid collision from those objects. Besides, weather-related concerns were also improved. However, these participants might easily encounter other people or objects in their daily navigation. Therefore, dynamic scenes in VR devices are essentials for improvements. Future studies could design a from-easy-to-hard trial to help participants become more acquainted with VR experimental protocols and reduce the burden of manipulation learning.

We successfully completed 9 participants to demonstrate the **feasibility** of PJVR, despite some participants reporting cybersickness during testing. Some improvements should be considered to enhance the completeness of the experiment. First, both the hardware and software should be refined. Issues such as low color saturation and limited screen resolution might interfere with human vision for navigating. Robust hardware and software design could facilitate smooth manipulation and reduce cybersickness [19]. Second, user-unfriendliness was also one of the issues in this study. It could be divided into two subcategories: the deprivation of walking and non-intuitive operations of the joysticks. Effective human navigation required cooperation of path information and vision-vestibular-proprioceptive integration [20]. If we replaced original walking functions with the handles, it would affect navigation in those subjects [21]. Concerning joystick operations, it took long time for our participants to get familiar with the manipulations. They might easily fall into a sense of fatigue and a feeling of deprivation of achievement. The manipulation of the blue light beam required precise movement of the arm and wrist. Moreover, some participants complained during or after the experiments that they were unable to select options even when the blue light beam visually aimed on the selection bars, while most of them were MCI due to AD participants. The software defects disrupted the participants that they were unable to maintain navigational strategies during the experiment. This eventually affected the final results and the completeness of each subject. Third, considering elderly individuals generally having fewer educational years, we must establish a simpler VR testing procedure with clear and specific tasks to minimize the testing difficulties. It was worth mentioning that the relationship between degraded navigational behavior in MCI due to AD patients and the PJVR testing remained unclear, strictly speaking, mainly due to the small sample size. These problems should be resolved in future studies to enhance the feasibility of the VR navigational tests.

To cope with those constraints, we proposed some suggestions for future studies. While entering answers, subjects could use voice input, or the researchers could fill in the blanks for subjects who answered verbally. The answer could also be entered by pressing only a single button to reduce difficulties learning joystick manipulations [8]. In addition, we could collect walking patterns from different subjects by artificial intelligence (AI) and global positioning system (GPS) within a specific range of time before a personalized test was conducted [5]. Adequate practice of VR tests before the formal tests is highly recommended. This might not only reduce the risks of dizziness during the tests, but also enhance their familiarity with the device. These methods might avoid other factors from affecting the test results, and the researchers could focus more on spatial-navigational abilities of the participants, which may eventually allow us to compare performances between RW and VR within the groups and to study further in the future.

Some studies considered that both egocentric and allocentric navigational strategies were involved in multiple spatial navigation tasks. It was difficult to design experiments that studied a certain navigation mode alone [12]. Many studies also suggested that AD patients had translational difficulties between egocentric and allocentric navigation [8,22–24]. In our research, we did not let out the content of the spatial map in advance, so that the participants had no time to remember and form a cognitive map. Instead, we provided a virtual map on the screen for the subjects to refer to. A little exploration was needed to acquire a general understanding of the spatial structure. Reasonably, the whole process was mainly testing their egocentric navigational abilities. However, to discuss such problems, we had no direct evidence due to our lack of brain-imaging data, which became one of the limitations of our research.

5. Conclusions

Our research established PJVR to observe human road recognizing abilities and their spatial navigation impairment. The result of *Lin*B supported our hypothesis, and furthermore, *Ang*C and *Lin*C had the potential to be the next indicators. This device provided a potential method to find out the differences of spatial navigational patterns between MCI due to AD patients and their cognitively unimpaired counterparts.

Ethics statement

The study was reviewed and approved by National Cheng Kung University Hospital Institutional Review Board for the Protection of Human Subjects, with the approval number: [ID: B-BR-110-046]. All participants provided their written informed consent form to participate in this study.

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Data availability

The data that have been used are confidential due to privacy issues.

CRediT authorship contribution statement

Chia-Hung Lai: Formal analysis, Methodology, Writing – original draft. **Ming-Chyi Pai:** Conceptualization, Funding acquisition, Investigation, Project administration, Software, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ming-Chyi Pai reports financial support was provided by National Science and Technology Council. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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