Neuropsychiatric Disease and Treatment

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Development and Validation of Paradigms Based on the Global-First Topological Approach for Alzheimer's Disease Severity Staging

Zhida Bian[1–3,*], Bo Wang[2,4,*], Xingqi Wu[3,5,6,*], Kai Wang[3,5–7], Yi Jiang[1,8]

[1]Anhui Medical University School of Basic Medicine, Hefei, 230032, People's Republic of China; [2]Institute of Artificial Intelligence, Hefei Comprehensive National Science Center, Hefei, 230088, People's Republic of China; [3]Anhui Province Key Laboratory of Cognition and Neuropsychiatric Disorders, Hefei, 230022, People's Republic of China; [4]State Key Laboratory of Brain and Cognitive Science, Institute of Biophysics, Chinese Academy of Sciences, Beijing, People's Republic of China; [5]Department of Neurology, the First Affiliated Hospital of Anhui Medical University, Hefei, 230022, People's Republic of China; [6]Collaborative Innovation Center of Neuropsychiatric Disorders and Mental Health, Hefei, 230022, People's Republic of China; [7]The School of Mental Health and Psychological Sciences, Anhui Medical University, Hefei, 230032, People's Republic of China; [8]State Key Laboratory of Brain and Cognitive Science, CAS Center for Excellence in Brain Science and Intelligence Technology, Institute of Psychology, Chinese Academy of Sciences, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Kai Wang, Department of Neurology, the First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, People's Republic of China, Email wangkai1964@126.com; Yi Jiang, Anhui Medical University School of Basic Medicine, Hefei, 230032, People's Republic of China, Tel +86 10 64879639, Fax +86 10 64856521, Email yijiang@psych.ac.cn

Introduction: Conventional methods like patient history, neuropsychological testing, cerebrospinal fluid examination, and magnetic resonance imaging are widely used to diagnose cases in the current clinical setting but are limited in classifying Alzheimer's disease (AD) stages. Patients with AD exhibit visual perception deficits, which may be a potential target to assess the severity of the disease according to visual paradigms. However, owing to the inconsistent forms of perceived objects, the defects of current visual processing paradigms often lead to inconsistent results and a lack of sensitivity and specificity.

Methods: We develop two paradigms based on global-first topological approach of visual perception, which avoids inconsistent results and lack of sensitivity and specificity owing to the inconsistent forms of perceived objects in traditional paradigms, delineate a unique detection strategy from perception organization (Experiment 1) and visual working memory (VWM) (Experiment 2).

Results: Except for the significant differences of the reaction times (RTs) between groups, significant differences were found when AD subjects recognize small figures due to the consistency of global and local figures in similarity test. The difference of RTs between recognizing global and local figures can be recognized in AD and mild cognitive impairment (MCI) group compared to healthy elderly (HE) in similarity test (Experiment 1). The memory capacity of AD patients was significantly lower than MCI group. Topological interference effect was observed in MCI and HE group, whereas MCI patients may have a greater difference trend in non-topological and topological changes than HE (Experiment 2).

Conclusion: Our paradigms provide a new strategy, which can assist clinical severity staging and linking topological approach of visual perception with pathophysiological processes in AD.

Keywords: Alzheimer's disease, visual perception deficits, paradigm, working memory, perceptual organization

Alzheimer's disease (AD) is characterized by deficits in the cognitive function of elderly individuals and is a continuous spectrum of disease, including mild cognitive impairment (MCI) and dementia, which interfere with independent daily functioning and quality of life. Clinically, predicting AD stage duration will contribute to the establishment of appropriate treatment plans in parallel with disease progression, thereby improving disease management.[1] Pathological testing of the cerebrospinal fluid biomarkers, amyloid β and tau protein, is regarded as the "gold standard"[2] for diagnosis, whereas staging of AD is a separate process and an easily accessible neuropsychological-based "gold standard" test does not exist.[2] Current standards of severity staging still depend on patient history and objective cognitive assessments

Received: 19 January 2024
Accepted: 23 May 2024
Published: 10 June 2024

performed by highly skilled neurologists.[3,4] However, there are large differences in the level of diagnosis from one clinician to another, and routine-scale assessment is greatly affected by non-objective aspects, cultural differences, education levels, and time-tolerance problems. Given this relatively imprecise assessment environment and the paucity of clinicians with sufficient diagnostic expertise in AD, the exploration of more sensitive, more accurate, and less subjective staging methods is particularly important.

Patients with AD exhibit visual perception deficits.[5] Multiple teams have attempted to stage the severity of AD through perceptual organization tasks[6,7] or visual working memory (VWM) paradigms across different dimensions (shape-color or color-position).[8–10] Despite the progress that has been made, only some paradigms incorporate graphic changes into the testing scope, and consider local geometric properties, such as collinearity and parallelism as primitives of visual representation, resulting in unclear patterns of graphic changes and difficulty in distinguishing their change attributes.[11–14] Moreover, previous studies simply regard "large and small shapes" as global and local properties in paradigms, lacking objective and accurate descriptions of experimental variables, resulting in inconsistent results.[15,16] Considering these factors, we surmise that the clinical potential of visual information processing paradigms is limited by the neglect of the significant impact of graphic properties, especially the role of graphic properties in the operational definition of perceptual objects, resulting in a lack of effective control variables.[9,10] To address these limitations, a new theoretical model for visual cognition and appropriate psychological variables is crucial for developing new methods to assist in severity staging.

Chen[13,14] established a seminal "global-first" theory, arguing that topological attributes are primitives of visual representation, and the visual process starts with large-scale properties and can be described by topological properties, which are the most appropriate psychological variables to describe the impact of brain diseases on cognitive function. In theory, establishing and developing effective experimental paradigms is expected to become an objective and accurate new method for the clinical assessment of cognitive function. To identify the AD status accurately, we selected two different paradigms for model development and validation: a VWM "topological-change interference effect (TCIE)" paradigm and a perceptual organization paradigm.

We developed a simpler and more straightforward method that differs from the traditional VWM paradigms.[8–10] Unlike the perceptual object inherited from the Gestalt tradition, topological properties are extracted during the initial phase of visual processing to form basic constraints on object coding. Whether new perceptual objects are generated by topological changes or potential perceptual objects are organized by topological resolution determines the allocation of VWM capacity. We pioneered the integration of perceptual object definitions into VWM from a topological perspective by setting a memory array with three conditions (no shape change, shape change, and topological-change) to identify patients with AD.[17]

With this perceptual organization paradigm, we hope to overcome the limitations of the original Navon paradigm according to the topological definition of the "basic unit of visual perception cognition".[18] Because the priority of topological properties determined by spatial adjacency and the precedent of perceptual organization of local shapes based on spatial adjacency determine global property processing,[19,20] we designed a new perceptual organizational paradigm using organizational principles as variables to determine the perceptual organizational ability of patients with AD at different stages.

The current situation regarding the visual processing of AD and its MCI precursors is based on the topological property perception theory. We first conducted a VWM "TCIE" test on healthy elderly people (HE), and MCI and AD patients. Second, we evaluated the perceptual organization paradigm of global and local visual processing under topological conditions. We hypothesized that the characteristics of visual processing in the sample would align with aging and disease progression, the VWM and perceptual organization of patients with MCI would be impaired, and more pronounced results would be observed in patients with AD.

Materials and Methods

Participants

This study was approved by the Ethics Committee of Anhui Medical University in China (2019H006), and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from the participants or their guardians.

29 HE participants, and 44 patients with MCI and 28 with AD aged between 55 and 85 years were recruited from the Memory Disorder Clinic of the Department of Neurology, the First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China, and an additional 26 college students were recruited as controls (YC). Diagnosis of AD was made according to the ICD-10 criteria by a consultant neurologist in conjunction with a multidisciplinary team assessment before recruitment. Patients also fulfilled the National Institute on Aging-Alzheimer's Association criteria, which considers cognitive performance in aging as a continuum of three stages, namely, cognitivelyunimpaired, mild cognitive impairment, and dementia, for probable or possible AD (NIA-AA).[21]

Validated Chinese versions of the Mini-Mental Status Examination (MMSE)[22], Montreal Cognitive Assessment (MoCA)[23] and Global Deterioration scale (GDS)[24] were administered. Patients with a history of uncorrected vision problems (eg, blindness, cataract, glaucoma, retinal detachment), language production problems were excluded. History of neurological disorders (eg, epilepsy, stroke, and neurodegenerative disorders other than AD) or depressive symptomatology (eg, participants with a diagnosis of major depression, major psychiatric disorder, or alcohol or substance abuse) were also viewed as exclusion criteria. Due to their inability to understand the content of the paradigm, patients with severe cognitive impairment (MMSE score <16) were excluded. The MCI and AD groups were administered donepezil (a widely used specific and reversible cholinesterase inhibitor in clinics) and all complied with the medication regimen. No intervention was administered in the HE group.

The three groups of participants (HE, MCI, and AD), which were homogeneous in terms of age, sex, and educational level, differed in their MMSE, MoCA and GDS scores, reflecting worse performances on the MMSE, MoCA and GDS in MCI and AD compared to HE group (Table 1).

Materials

Stimuli were displayed individually on a 19-inch LCD (Dell INSPIRON BOE093F Display; Dell, Round Rock. TX, USA) (refresh rate 60 Hz) with a resolution of 1024 × 768 pixels using MATLAB 2013a with Psychophysics Toolbox (Mathworks, Natick, MA, USA) extensions. All participants were seated in an acoustically insulated and well-illuminated room, approximately 70 cm to the computer screen.

Perceptual Organization Task

The perceptual organization task was administered with a large arrow and a triangle formed by a small arrow or triangle. The large shapes measured 4.4 cm in height and 3.8 cm in width (vertical and horizontal visual angles 3.6° × 3.1°, respectively), while the small shapes were 0.4 cm high and 0.3 cm wide (vertical and horizontal visual angles 0.25° × 0.33°, respectively)(Set A in Figure 1a). The second set of stimuli consisted of the first set of stimuli on a background graphic showing "+". The size and contrast of "+" were the same as those of the small shapes, and the distance between "+" and adjacent small shapes was the same as that between adjacent two small shapes. The size of each figure in the second group of stimuli, including the background "+", was 5.6 cm × 4.8 cm (vertical and horizontal visual angles 4.6° × 3.9°, respectively) (Set B in Figure 1a). The composite stimulus only appeared in the center of the field of vision,

Table 1 Comparison of Demographic Variables Between Different Groups

Variables	HE	MCI	AD	Intra-Group *p* value	
				F	*p*
Age	62.17±7.39	62.89±9.57	67.08±8.30	2.63	0.078
Education years	11.72±3.31	10.56±3.66	9.88±3.73	1.89	0.157
Gender	1.41±0.50	1.42±0.50	1.65±0.48	2.15	0.123
MMSE	28.93±1.03	25.72±2.21	20.69±2.60	111.69	0.000**
MoCA	27.59±1.90	20.72±3.00	14.00±2.67	187.677	0.000**
GDS	1.21±0.41	2.40±0.50	3.29±0.60	121.551	0.000**

Notes: **$p < 0.01$. Comparisons between groups were assessed by the ANOVA test.
Abbreviations: MMSE, Mini-Mental Status Examination; MoCA, Montreal Cognitive Assessment; GDS, Global Deterioration scale; HE, Healthy elderly; MCI, Mild cognitive impairment; AD, Alzheimer' s disease.

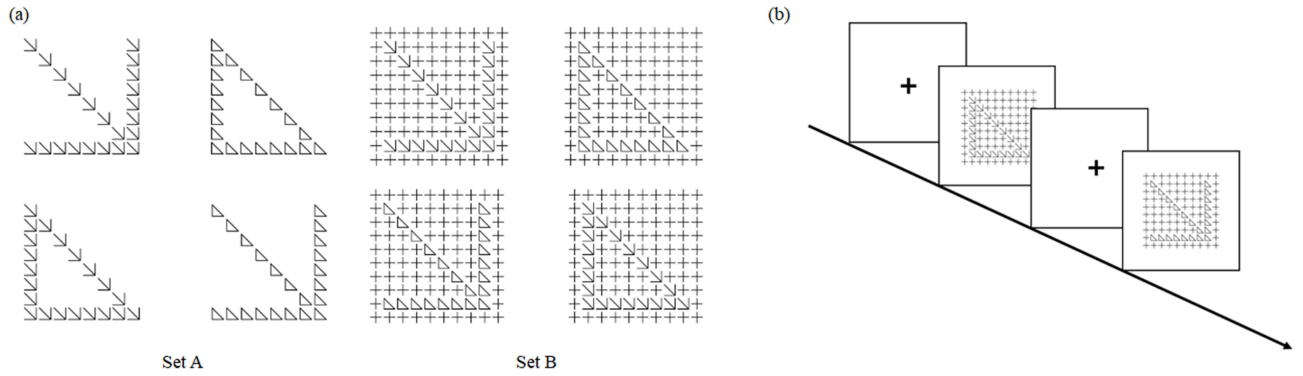

Figure 1 (**a**) Set A is dominated by proximity organizations; Set B adds a background image around Set A, comparing proximity organizations to make similarity organizations dominant. (**b**) The task is to determine whether the large and small shapes are triangles or arrows, respectively.

and the center of the composite stimulus coincided with the fixation point, whereas the size of the fixation was 0.4 cm × 0.5 cm. Both sets of stimuli included the task of identifying large and small pieces of graphics. Before the 64 formal experiments, each group of participants performed eight exercises. The middle fingers of the left and right hands were tested to respond by pressing the "triangle" and "arrow" keys on a special double-key keyboard. In the experiment, the participants were required to focus on an observation point and press a button to respond as soon as possible, provided that the report was accurate. The experimental setup is illustrated in Figure 1b.

Visual Working Memory Task

There was a 9.8° × 7.3° region on a gray background at a viewing distance of 70 cm to present all stimuli. Each item, which was randomly placed in the background of a given array, was separated from the others by at least 2° (center-to-center). Seven highly discriminable colors were randomly selected for each square using RGB values: black (0, 0, 0), red (255, 0, 0), green (0, 255, 0), blue (0, 0, 255), yellow (255, 255, 0), magenta (255, 0, 255), and white (255, 255, 255), whereas each color for both the memory array and the test array appeared no more than twice. Each stimulus subtended a visual angle of 0.95° × 0.95°. Three groups of stimulus patterns, including different topological transition patterns, were used in the experiment (Figure 2a). In addition, the non-topological changes that included massive shape deformations

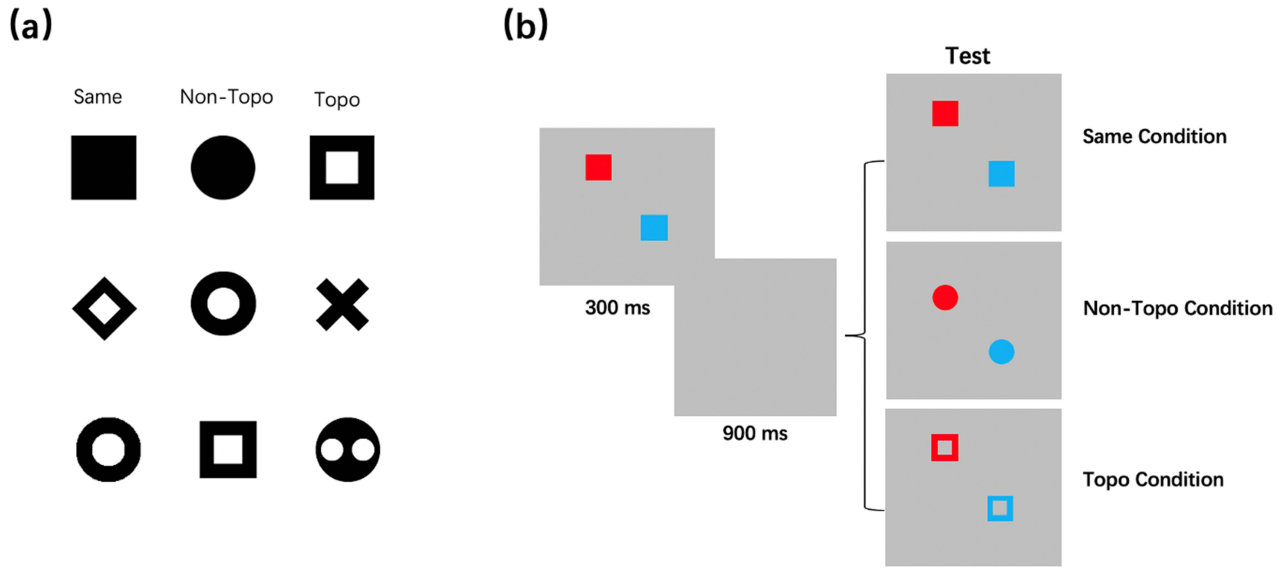

Figure 2 (**a**) Schematic depiction of the stimulus groups for Experiment 2 and (**b**) Schematic description of Experiment 2, the no-change pattern was presented in the first display and the no shape change, the non-topological change, or the topological change pattern was presented in the second display randomly.

involved in various local feature changes were carefully controlled in the experiment. Although they looked phenomenally different, these stimulus figures were the topological equivalent to each other.

The experimental setup is illustrated in Figure 2b. Each trial began with a 500-ms fixation to warn the participants of the start of a trial. Subsequently, a 300-ms sample display containing two- or three-colored items was presented, followed by a 900-ms blank interval. Finally, a test array was presented on the screen until a response was obtained. The number of memory items was two or three, and seven different colors appeared only once in one trial. Thirty-six trials for each condition with each stimulus resulted in 144 trials per participant, appearing randomly within the four blocks. Participants were encouraged to explicitly answer whether a color changed between the memory and test arrays while ignoring whether the shape changed, which would impair their performance if they attended to that aspect. Participants were instructed to respond accurately using two alternative forced-choice responses on a response keyboard at the end of each trial.

Statistical Analysis

Independent-samples t-tests were used to compare the differences in demographics (age, sex, and education) and clinical and cognitive data between groups. A multiple variable analysis of repeated measures of variance (ANOVA) was used to analyze the data on accuracy from the VWM experiments under two memory load conditions (n = 2 and n = 3), which involved three types of VWM stimuli (same, non-topological change, and topological change) in the groups.

The mean of raw RTs was calculated using multiple variable analysis of repeated measures with participants as the random factor, with a fixed between-participant factor and two fixed within-participant factors, establishing a compound symmetry variance-covariance matrix. The independent variables were the within-participants factor task (global/local) and stimulus consistency (consistent/inconsistent), whereas the between-participants factor group (YC/HE/MCI/AD) view was random.

All data were analyzed using SPSS software (version 22.0; IBM Corp., Armonk, NY, USA). Graphs were plotted using GraphPad Prism 7 software (GraphPad Software, Inc. San Diego, CA, USA). The *p*-value of 0.05 was considered statistically significant and all tests were two-tailed.

Results

Perceptual Organization Task

Repeated measure ANOVA was used to analyze the average RTs and accuracy of the test results. The analysis of variance was conducted using four sets of inter-subject factors and three stimulus types: (a) background "+" for complex stimuli, (b) global or local, and (c) consistency of graphics. RTs of more than 2500 ms or more than 3 SD from the mean in each condition for each individual were removed from the analysis (<5%). Mean RTs and accuracy were analyzed for each condition. There was no significant difference in the accuracy among the participants in each group under the various conditions ($p > 0.05$). The RTs results are shown in Figure 3 and Table 2.

In the proximity task, significant differences was observed between the HE and YC groups in terms of the recognition of all schema patterns of RTs (F = 49.12, partial $\eta^2 = 0.56$, $p < 0.001$). The interaction of type*consistency had

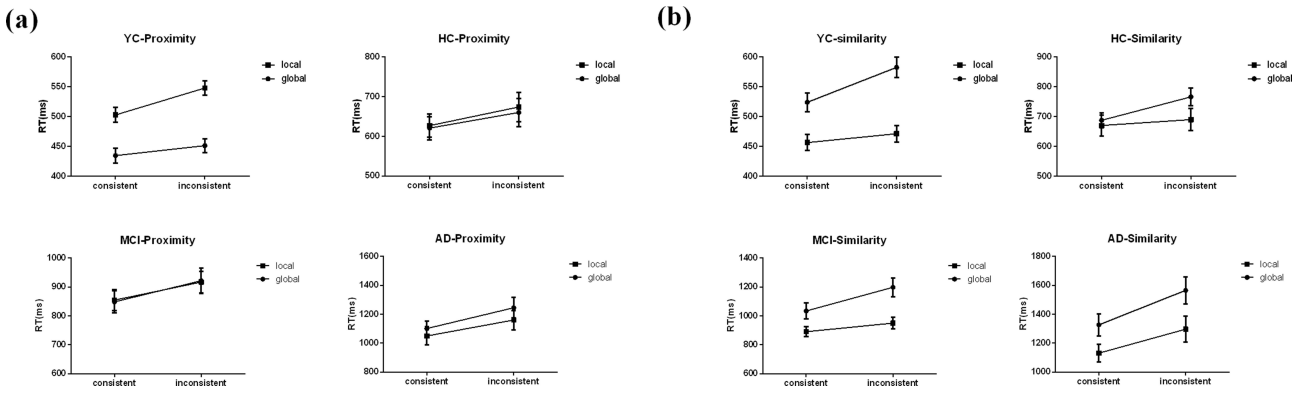

Figure 3 Estimated mean values (and standard error) of RTs (in ms) for each group, task, and consistency in the perceptual organization task; (**a**) Set A is dominated by proximity organizations and (**b**) Set B is dominated by similarity organizations.

Table 2 RTs of Perceptual Organization Under Different Tasks in Different Groups

		Proximity				Similarity			
		Global		Local		Global		Local	
		Consistent	Inconsistent	Consistent	Inconsistent	Consistent	Inconsistent	Consistent	Inconsistent
Group	*YC*	439.04±62.03	453.72±58.53	502.84±62.26	548.00±59.39	524.08±77.22	582.80±85.67	456.60±66.83	471.46±69.35
	HE	601.77±116.67	635.35±135.84	627.03±153.61	674.04±191.77	687.96±129.59	766.56±150.26	668.30±139.81	683.74±138.04
	MCI	846.95±249.52	922.76±291.86	852.19±242.02	911.29±246.68	1017.78±354.73	1158.74±343.14	887.95±235.99	942.93±264.45
	AD	1101.67±263.89	1245.04±362.11	1081.57±363.73	1180.04±353.85	1415.64±486.75	1675.14±608.88	1131.57±325.93	1297.14±470.10
F		49.12				43.85			
p_c		0.001**				0.001**			
ηp^2		0.56				0.53			

Notes: p_c: after the Bonferroni correction; **$p < 0.01$.
Abbreviations: YC, Young control, HE, healthy elderly, MCI, mild cognitive impairment; AD, Alzheimer's disease.

a significant impact on the RTs in the YC group ($p < 0.001$), whereas no significant impact was found in the other three elderly groups (HE, MCI, AD groups). RTs showed a significant type main effect in the YC group ($p < 0.001$). The consistency condition also showed a significant type main effect in the YC group ($p < 0.001$), and further analysis found the consistency of patterns had a significant effect on the recognition of local patterns, but no significant effect on the recognition of large patterns. There were significant intra-group differences in RTs among the three groups of elders (HE, MCI, AD groups) with consistency as a main effect ($p < 0.05$), indicating that the consistency of patterns had a significant impact on the RTs for recognition patterns in the three groups. There were no significant type main effects for condition in the elderly groups ($p > 0.05$). Each stimulus type was double-checked for accuracy among the three elderly groups, but no significant differences were found.

Significant differences were also observed between the elderly groups and the YC group in the RTs of all composite patterns in the similarity task (F = 43.85, partial $\eta^2 = 0.53$, $p < 0.001$). The type *consistency interaction had a significant impact on the RTs of all groups except for the AD group ($p < 0.001$), and there were significant differences in the RTs among the four groups, with type as the main effect ($p < 0.001$). Although a significant difference in RTs for the recognition of graphics was observed in the HE group when global and local graphics were inconsistent, the difference in RTs was not significant when graphics were consistent. Significant differences in RTs were observed among the groups, with consistency as the main effect ($p < 0.001$). Although further analysis found that consistency in size patterns only had a significant impact on the recognition of large patterns among the YC, HE, and MCI groups ($p < 0.001$), there was no significant effect on the recognition of small patterns among the groups ($p > 0.05$). However, the consistency of size patterns had a significant influence on the RTs in recognizing both global and local patterns in the AD group (all $p < 0.001$).

Visual Working Memory Task

The accuracy of the elderly groups is shown in Figure 4 and Table 3. Variance analysis was used to analyze the accuracy of the test array memory, and violations of sphericity were corrected using the Greenhouse–Geisser correction. When n = 2 or n = 3, the inter-group comparisons showed significant differences in accuracy between the groups under different change conditions. Compared with the HE and MCI groups, working memory capacity was significantly reduced in the AD group.

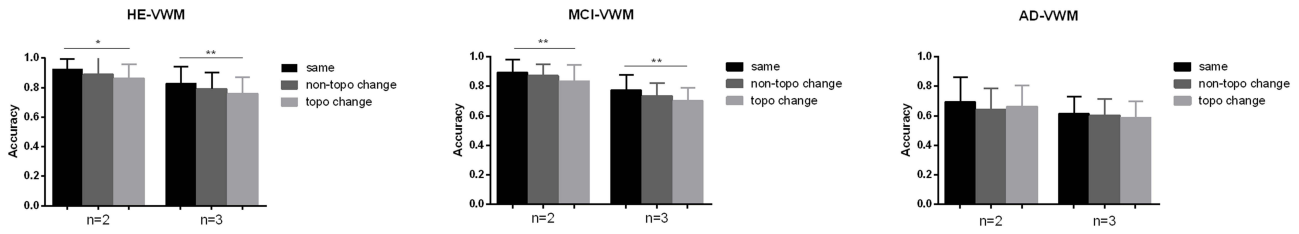

Figure 4 The differences of VWM levels in different size conditions compared to different groups; *p < 0.05. **p < 0.01.

Table 3 Comparison of Visual Working Memory Variables Between Different Groups

Groups	Number	Same	Non-Topological Change	Topological Change	Inter-Group *p* value		
					F	*p*	*Partial Eta²*
HE	2	0.926±0.067	0.890±0.109	0.865±0.092	6.290	0.003**	0.183
	3	0.828±0.116	0.793±0.110	0.761±0.110	3.990	0.024*	0.125
MCI	2	0.894±0.085	0.872±0.078	0.835±0.110	8.193	0.001***	0.167
	3	0.774±0.102	0.735±0.087	0.702±0.087	7.369	0.001***	0.152
AD	2	0.694±0.168	0.644±0.143	0.663±0.141	2.587	0.086	0.101
	3	0.616±0.116	0.600±0.113	0.589±0.109	0.531	0.091	0.023

Notes: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Comparisons in groups were assessed by the ANOVA test.
Abbreviations: HE, healthy elderly, MCI, mild cognitive impairment; AD, Alzheimer's disease.

The shape-change condition showed a significant main effect in both the HE and MCI groups, regardless of whether n = 2 or n = 3. Furthermore, Bonferroni post-hoc tests showed no significant differences in accuracy between the different conditions. The intra-group difference in the shape-change condition was significant in the HE group (p_2 = 0.003/p_3 = 0.024), whereas the MCI group also showed significant differences in intra-subject accuracy (p_2 = 0.001/p_3 = 0.001) (Table 3). Further analysis also showed a significant difference in accuracy between the topological change condition and no change condition, with non-topological change accuracy between topology change and no shape change accuracy in the two groups under different set sizes (n = 2 and n = 3). Compared with the HE group, the MCI group showed a greater trend towards accuracy differences between non-topological and topological changes (p_2 = 0.0502/p_3 = 0.1188).

Discussion

In order to improve the accuracy of AD diagnosis and staging by neurologists, we developed new detection paradigms based on the global-first topological approach of the visual perception theory to evaluate and accurately quantify the severity of cognitive impairment in patients.

AD Patients Showed Enhanced Consistency Bias to Local Letter in Similarity Task

Our new perceptual organization paradigm based on "global-first" theory avoided the common problems due to the lack of objective and accurate descriptions of the experimental variables in the classic Navon paradigm. Significant differences in RTs were found among the four groups for different tasks, indicating a significant difference in the processing speed of visual perceptual organization among patients with neurodegenerative diseases and varying degrees of visual perceptual organization damage between patients with MCI and patients with AD.

In the similarity condition test, the primary finding of this study was the consistency of global and local figures, which significantly influenced the identification of small figures in patients with AD. Owing to the composite stimuli composed of small images with "+" presented in the background, the similarity between small images becomes the main factor determining the organization of small images. The priority of local property processing determines that healthy young participants have faster RTs in identifying small patterns than large ones, and the consistency of patterns causes less interference in identifying small patterns.[25] In our study, the consistency of figure patterns had a significant impact on the RTs of AD patients in recognizing small patterns. The results of a similar study support our results with the finding that although participants were unable to perceive global shapes, they did exhibit global interference during local task processing, revealing the implicit processing of global shapes.[26] The same finding was obtained with our participants with AD, who revealed a possible global covert interference, which may have significance for the stage differentiation between MCI and AD.

It is noticing that, except for the HE group, the other two elderly groups did not exhibit the priority for local processing in size pattern recognition RTs like young controls. There is currently no clear explanation for this RTs variation. We speculate that, on the one hand, HE participants exhibited significant perceptual deficits in local geometric

visual perception, leading to a gradual loss of priority in their local processing, which also explains why healthy middle-aged and elderly people do not exhibit significant local dominance effects in similarity task.[27] On the other hand, previous studies have suggested that the process of grouping scene construction elements is severely impaired in patients with dementia, resulting in difficulties in recognizing global shapes, which is probably the reason for the differences in RTs in identifying patterns in patients with MCI and AD.[28] In other words, our results may be significant for community screening of cognitive impairment.

In the proximity test, YCs showed faster RTs in global patterns, whereas HE participants, patients with MCI and patients with AD did not show significant intra-group differences in RTs for identifying patterns in proximity tasks, which confirmed our theory. When composite stimuli are presented on a blank background, the perceptual organization between small images is mainly determined by the proximity of local patterns. Thus, the behavioral results of YCs show priority in global property processing.[20,29,30] The loss of significant global advantages in all elderly groups could reflect the gradual disappearance of the global advantage effect based on the proximity between patterns according to degenerative changes in the brain, which is related to the results of the traditional Navon paradigm.[31]

Significant bidirectional interference (ie, slower RTs in inconsistent versus consistent trials in both tasks) was also found in elderly individuals with physiological and pathological aging in the proximity test, indicating that physiologically- and pathologically-aging subjects are more susceptible to interference factors than YCs, whereas healthy young subjects only show a strong interference effect on identifying local patterns. Similar to the inhibition-deficit theory of aging, attention to irrelevant-level interference is not independent of participation, which suggests that it could reflect an age- and pathological-related decline in the capacity to inhibit distractors.[32,33] In other words, physiological or pathological brain atrophy may lead to a dysfunction in proximity organization and a decrease in anti-interference ability.

Notably, one participant with MCI and several participants suffered from AD were unable to identify the global level of the patterns despite ensuring comprehension and repeated practice in this experiment. It has been reported on the inability of AD patients to perceive global graphics by other authors, which could be regarded as a serious obstacle to the process of grouping scene construction elements.[26,34] In addition, similar to the results of the Navon experiment, we found inter-group differences in the RTs for identifying patterns in different proximity and similarity tasks, which is of great significance for AD community screening and severity staging.

AD Patients Showed Lower Memory Capacity Compared to MCI

Topological invariance refers to the invariance of connectivity, number of holes, and internal and external relationships under continuous deformation (including stretching and bending). According to our team's previous study, when the topological properties of the item changed, the continuity of an object was interrupted and this caused the stimulus to be perceived as a new item, thereby weakening the repetition-benefit effect. However, when the second storage array underwent moderate feature changes, the repeated benefit effect on color memory of YCs is not significantly affected.[35] Compared with our previous study, the memory capacity of HE individuals and patients with MCI was significantly reduced, and a significant TCIE was observed only after the image presentation time was significantly prolonged, which is consistent with our previous speculation.[17]

In comparison, when the second storage array underwent moderate feature changes, the repeated-benefit effect of color memory in healthy older adults was also affected to a certain extent, which was weaker than the influence of topological attribute interference, although this trend was not statistically significant.[35] In addition, we found a trend towards accuracy differences non-topological and topological conditions in the MCI group, although this trend was not significant. This may be related to the relatively small number of trials we used, but it does have some significance for the conjecture that patients with MCI may show greater topological interference effects. According to another study by our team, although object continuity survives a wide range of non-topological changes, elderly people still show certain difficulties in distinguishing non-topological change patterns because local geometrical visual perception clearly deteriorates with age, which explains why non-topological changes also interfere with the repetitive advantage effect in elderly people.[27]

Notably, despite the ensured comprehension and repeated practice in this experiment, the accuracy under different conditions was significantly decreased in patients with AD, whereas no significant repetitive interference effect was observed in these patients. This may be due to the significant decrease in the working memory capacity, lack of hyperactivation, and significantly poor task performance in task load associated with AD, indicating a compensatory

deficiency due to more severe neurodegeneration.[36] In other words, this result significantly distinguishes between MCI and AD in terms of memory capacity and disease stage.

We did not observe a significant decrease in VWM capacity in patients with MCI, which was somewhat different from our expectations. On the one hand, considering our relatively small number of trials, there was a certain impact on the final accuracy rate. On the other hand, some studies have found that patients with MCI show a certain degree of working memory compensation. These studies have shown is no difference in bilateral PFC activation between subjects with MCI and HE subjects under lower task loads. Neurocompensation in the form of overactivation is evident in patients with MCI with a moderate task load.[36,37]

This study has some limitations. The case-control population in which sub-populations that were either cognitively normal or had a diagnosis were pre-selected in advance, cannot fully represent the standard clinical decision-making situation faced by neurologists. Although it cannot be directly applied to the current state, our method serves as the first step towards the establishment of comprehensive framework for auxiliary diagnosis and staging of AD. It is worth noting that our paradigms have significant potential for assessment of diagnosis and severity staging in AD. In the future, we will increase test arrays numbers and samples in VWM task and the reasons for some patients who cannot recognize the shape of global shapesin in proximity tasks and more patients who cannot recognize global shapes in similarity tasks still need further research in perceptual organization tasks. We plan to conduct correlation studies using imaging data, non-imaging data, and biological indicators to explore their mechanisms and establish a comprehensive framework.

Conclusion

In summary, our model intuitively reflects the differences and changes in healthy subjects of different age groups and patients with AD of different periods, overcoming the limitations of traditional diagnostic staging tools, and helping neurologists diagnose and stage diseases in the clinical study, as well as guiding the formulation of auxiliary treatment plans. Our paradigm demonstrates the enormous transformative potential of the global-first topological approach of the visual perception theory for the staging of AD. Further validation could lead to improvements in the accurate staging of diseases. This paradigm may have application for large-scale community screening of older adults and resulting in improvements in patient outcomes.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Doody RS, Pavlik V, Massman P, et al. Predicting progression of Alzheimer's disease. *Alzheimers Res Ther*. 2010;2(1):2. doi:10.1186/alzrt25
2. Lloret A, Esteve D, Lloret MA, et al. When does Alzheimer's disease really start? The role of biomarkers. *Int J Mol Sci*. 2019;20(22):5536. doi:10.3390/ijms20225536
3. Frisoni GB, Fox NC, Jack CR, Scheltens P, Thompson PM. The clinical use of structural MRI in Alzheimer disease. *Nat Rev Neurol*. 2010;6(2):67–77. doi:10.1038/nrneurol.2009.215
4. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):263–269. doi:10.1016/j.jalz.2011.03.005
5. Jack CR, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):257–262. doi:10.1016/j.jalz.2011.03.004
6. Alescio-Lautier B, Michel BF, Herrera C, et al. Visual and visuospatial short-term memory in mild cognitive impairment and Alzheimer disease: role of attention. *Neuropsychologia*. 2007;45(8):1948–1960. doi:10.1016/j.neuropsychologia.2006.04.033
7. Liu C, Sha S, Zhang X, et al. The time course of perceptual closure of incomplete visual objects: an event-related potential study. *Comput Intell Neurosci*. 2020;2020:8825197. doi:10.1155/2020/8825197
8. Parra MA, Abrahams S, Fabi K, et al. Short-term memory binding deficits in Alzheimer's disease. *Brain*. 2009;132(Pt 4):1057–1066. doi:10.1093/brain/awp036
9. Liang Y, Pertzov Y, Nicholas JM, et al. Visual short-term memory binding deficit in familial Alzheimer's disease. *Cortex*. 2016;78:150–164. doi:10.1016/j.cortex.2016.01.015
10. Parra MA, Sala SD, Abrahams S, et al. Specific deficit of colour-colour short-term memory binding in sporadic and familial Alzheimer's disease. *Neuropsychologia*. 2011;49(7):1943–1952. doi:10.1016/j.neuropsychologia.2011.03.022
11. Zhou K, Luo H, Zhou T, et al. Topological change disturbs object continuity in attentive tracking. *Proc Natl Acad Sci U S A*. 2010;107(50):21920–21924. doi:10.1073/pnas.1010919108
12. Huang Y, Zhou T, Chen L. The precedence of topological change over top-down attention in masked priming. *J Vis*. 2011;11(12):9. doi:10.1167/11.12.9
13. Chen L. Topological structure in visual perception. *Science*. 1982;218(4573):699–700. doi:10.1126/science.7134969

14. Chen L. The topological approach to perceptual organization. *Vis Cogn*. 2005;12(4):553–637. doi:10.1080/13506280444000256
15. Bouhassoun S, Poirel N, Hamlin N, et al. The forest, the trees, and the leaves across adulthood: age-related changes on a visual search task containing three-level hierarchical stimuli. *Atten Percept Psychophys*. 2022;84(3):1004–1015. doi:10.3758/s13414-021-02438-3
16. Muller-Oehring EM, Schulte T, Raassi C, et al. Local-global interference is modulated by age, sex and anterior corpus callosum size. *Brain Res*. 2007;1142:189–205. doi:10.1016/j.brainres.2007.01.062
17. Wei N, Zhou T, Zhuo Y, et al. Topological change induces an interference effect in visual working memory. *J Vis*. 2021;21(10):4. doi:10.1167/jov.21.10.4
18. Han S, Weaver JA, Murray SO, et al. Hemispheric asymmetry in global/local processing: effects of stimulus position and spatial frequency. *Neuroimage*. 2002;17(3):1290–1299. doi:10.1006/nimg.2002.1255
19. Chen L, Zhang S, Srinivasan MV. Global perception in small brains: topological pattern recognition in honey bees. *Proc Natl Acad Sci U S A*. 2003;100(11):6884–6889. doi:10.1073/pnas.0732090100
20. Wang B, Zhou TG, Zhuo Y, et al. Global topological dominance in the left hemisphere. *Proc Natl Acad Sci U S A*. 2007;104(52):21014–21019. doi:10.1073/pnas.0709664104
21. Jack CR, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535–562. doi:10.1016/j.jalz.2018.02.018
22. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189–198. doi:10.1016/0022-3956(75)90026-6
23. Hong Y, Zeng X, Zhu CW, et al. Evaluating the Beijing Version of Montreal cognitive assessment for identification of cognitive impairment in Monolingual Chinese American Older Adults. *J Geriatr Psychiatry Neurol*. 2022;35(4):586–593. doi:10.1177/08919887211036182
24. Rodriguez-Hidalgo E, García-Alba J, Novell R, et al. The Global Deterioration Scale for Down Syndrome Population (GDS-DS): a rating scale to assess the progression of Alzheimer's Disease. *Int J Environ Res Public Health*. 2023;20(6):5096. doi:10.3390/ijerph20065096
25. Han S, Fan S, Chen L, et al. On the different processing of wholes and parts: a psychophysiological analysis. *J Cogn Neurosci*. 1997;9(5):687–698. doi:10.1162/jocn.1997.9.5.687
26. Slavin MJ, Mattingley JB, Bradshaw JL, et al. Local-global processing in Alzheimer's disease: an examination of interference, inhibition and priming. *Neuropsychologia*. 2002;40(8):1173–1186. doi:10.1016/S0028-3932(01)00225-1
27. Gan J, Wang N, Li S, et al. Effect of age and refractive error on local and global visual perception in Chinese children and adolescents. *Front Hum Neurosci*. 2022;16:740003. doi:10.3389/fnhum.2022.740003
28. Kurylo DD, Allan WC, Collins TE, et al. Perceptual organization based upon spatial relationships in Alzheimer's disease. *Behav Neurol*. 2003;14 (1–2):19–28. doi:10.1155/2003/856309
29. Han S, Xiao F. Several factors affecting the processing of global and local properties in visual composite stimuli. *Acta Psychologica Sinica*. 1999;31(3):10.
30. Navon D. Forest before trees: the precedence of global features in visual perception. *Cognitive Psychol*. 1977;9(3):353–383. doi:10.1016/0010-0285(77)90012-3
31. Alvarez-San Millan A, Iglesias J, Gutkin A, Olivares EI. Progressive attenuation of visual global precedence across healthy aging and Alzheimer's disease. *Front Aging Neurosci*. 2022;14:893818. doi:10.3389/fnagi.2022.893818
32. Hasher L, Lustig C, Zacks RT, et al. Inhibitory mechanisms and the control of attention . *Variation in Working Memory*. Eds. ; 2007:227–249.
33. Tsvetanov KA, Mevorach C, Allen H, et al. Age-related differences in selection by visual saliency. *Atten Percept Psychophys*. 2013;75 (7):1382–1394. doi:10.3758/s13414-013-0499-9
34. Piccini C, Lauro-Grotto R, Del Viva MM, et al. Agnosia for global patterns: when the cross-talk between grouping and visual selective attention failS. *Cogn Neuropsychol*. 2003;20(1):3–25. doi:10.1080/02643290244000167
35. Wei N, Zhou T, Zhang Z, Zhuo Y, Chen L. Visual working memory representation as a topological defined perceptual object. *J Vis*. 2019;19(7):12. doi:10.1167/19.7.12
36. Lin P, LaMonica HM, Naismith SL, et al. Memory compensation strategies in older people with mild cognitive impairment. *J Int Neuropsychol Soc*. 2020;26(1):86–96. doi:10.1017/S1355617719000912
37. Ung WC, Yap KH, Ebenezer EGM, et al. Assessing neural compensation with visuospatial working memory load using near-infrared imaging. *IEEE Trans Neural Syst Rehabil Eng*. 2020;28(1):13–22. doi:10.1109/TNSRE.2019.2956459