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Relationship between neuropsychological test scores and hippocampal atrophy in non-demented Japanese older adults

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ABSTRACT

Background: It is essential to detect morphological changes in the brain prior to the onset of cognitive decline. Although hippocampal volumes have been reported to be correlated with scores on neuropsychological tests, this relationship is still unclear among Japanese non-demented older adults. Thus, this exploratory retrospective study aimed to identify neuropsychological tests that correlate with the degree of hippocampal atrophy in Japanese non-demented older adults.

Methods: Thirteen non-demented Japanese older adults aged 71.2 ± 5.2 years were included. Hippocampal atrophy was evaluated by assessing the participants' MRI scans using the voxel-based specific regional analysis system for Alzheimer's disease (VSRAD) software. Spearman's partial correlation analyses were conducted to reveal relationships between VSRAD scores and neuropsychological test scores, including Raven's Colored Progressive Matrices test (RCPM), the Standard Verbal Paired Associate Learning test (SP-A), and the Trail Making Test (TMT) scores by controlling for age, sex, and years of education.

Results: The Spearman's partial correlation analysis results revealed that there were significant correlations between the degree of hippocampal atrophy and RCPM (rho = -0.691, p = 0.027), TMT part B (rho = 0.823, p = 0.003), and the related SP-A test scores (rho = -0.663, p = 0.027).

Conclusions: Our results indicate that neuropsychological tests, particularly the TMT part B, might be used in assessing the degree of hippocampal atrophy in non-demented Japanese elderly individuals and should be studied further in the future to develop screening methods to detect brain atrophy.

1. Introduction

There is growing evidence that lifestyle changes or improvements in education and nutrition could potentially reduce the incidence of Alzheimer's disease (AD) [1]. It has also been reported that multidomain interventions, such as exercise and diet, may increase or maintain cognitive health [2]. In a global aging society, preventive interventions or early detections of cognitive decline in older adults have become important. To promote preventive intervention, early detection or methods to assess the risk of cognitive decline are needed, especially in Japan, where the global cost of dementia is expected to reach JPY 24.3 trillion by 2060 [3].

Cognitive decline is typically assessed using neuropsychological tests. Interestingly, atrophy of medial temporal lobe structures, including the hippocampus, has been reported prior to cognitive decline in AD [4,5], mild cognitive impairment (MCI) [5,6], and in non-demented elderly individuals [7]. Therefore, the assessment of morphological atrophy may be important to identify whether elderly individuals are at risk of cognitive decline. The voxel-based specific regional analysis system for Alzheimer's disease (VSRAD) [8] is a free software that has recently been widely used to supplement AD diagnoses and health checkups in Japanese clinical settings [9]. VSRAD

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quantitively assesses the degree of hippocampal atrophy as observed on magnetic resonance imaging (MRI) and computes atrophy as a relative value compared to that of healthy individuals, which makes it easy to interpret. A value ≥ 2 indicates suspected AD. VSRAD can also quantitatively assess regional and hippocampal areas with fewer errors than conventional manual segmentation [10]. However, this is a costly and time-consuming method, especially for people without subjective and objective cognitive impairment.

Many studies have reported correlations between neuropsychological test scores and hippocampal volume in non-demented elderly individuals [11–15]. These tests could be a viable option not only to detect cognitive decline but also to predict the early stages of brain atrophy. Although the Mini-Mental State Examination (MMSE) is widely used to detect cognitive decline, it has low sensitivity for discrimination between MCI patients and cognitively healthy adults [16] and has a ceiling effect in non-demented elderly individuals [15]. Moreover, its correlation with hippocampal volume is reportedly weak [14,15]. Therefore, identifying neuropsychological tests that assess functions related to cognitive declines, such as visuospatial perception [17] and executive function [18], in addition to memory, is essential as they may reveal underlying hippocampal atrophy. Previous studies have demonstrated mild to moderate correlations between neuropsychological test scores and hippocampal volume or atrophy [11–15]. However, only limited studies have assessed this in Japanese non-demented elderly populations [15]. The current retrospective study aimed to explore whether neuropsychological test scores are correlated with hippocampal atrophy in non-demented Japanese older adults, leading to the development of future screening methods to predict hippocampal atrophy.

2. Methods

2.1. Participants

Participants who underwent cognitive health checkups between October 2016 and July 2018 at Kakeyu Hospital were screened. During the cognitive health checkups, participants underwent MRI, and neuropsychological tests were administered by experienced clinical psychologists, including the Raven's Colored Progressive Matrices test (RCPM) [19] to assess their intelligence and visuospatial function; the Trail Making Test (TMT) parts A and B [20] to assess attention and executive function; and the Standard Verbal Paired Associate Learning test (SP-A) [21] to assess verbal memory function. Clinicians also conducted physical medical examinations. Based on the results of the MRI and neuropsychological tests, participants with suspected dementia were recommended to undergo a detailed examination and transfer to different hospitals that specialized in the treatment of dementia. In this study, we included older adults with no prior diagnosis of dementia according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria [22] and no abnormal MRI findings.

This retrospective study was conducted in accordance with the Declaration of Helsinki guidelines and approved by the Medical Ethics Committee of Kakeyu Hospital (approval number: 2018049). Informed consent was not obtained owing to the retrospective study design.

2.2. Neuropsychological testing

2.2.1. Raven's Colored Progressive Matrices Test

The RCPM test was used to assess the participant's intelligence and visuospatial function without assessing their verbal ability [19]. RCPM scores have been reported to correlate with brain activity in specific regions in AD patients [23], and disease progression is indicated by a lower score [24]. The test requires participants to analyze color, form, and linear slope and to select one picture out of six that has the same pattern as a reference picture. Three picture sets (A, B, and AB) were used, each including 12 pictures, for a total of 36 pictures. A score of <24 out of 36 was indicative of declining intelligence. We recorded the number of correct answers per set, for a total of three sets for analysis.

2.2.2. Trail Making Test parts A and B

The TMT is one of the most commonly used neuropsychological tests in clinical settings for screening neurodegenerative disease among older adults [25] and among older patients with dementia in research settings [26]. It is used to assess executive (or task-switching) and attention functions [20,27] and is composed of two parts—A and B. Part A required participants to link randomly numbered points from 1 to 25 on paper, in ascending order, as fast as possible. Part B required the participants to link randomly allocated numbers and letters alternately in ascending order, as fast as possible. The examiner measured the time taken to complete each part and the number of errors made in each part. For our analysis, we recorded the time taken to complete each part.

2.2.3. Standard Verbal Paired Associate Learning Test

The S-PA was developed by the Japan Advanced Brain Dysfunction Society to assess verbal memory function [21] and used in research settings in Japan [28]. It comprises 10 pairs of related or unrelated words presented to the participant. The examiner read a combination of 10 semantically related words or 10 irrelevant words with no semantic relation, which was memorized by the participants. The examiner then presented the first word, and the participants answered the relevant word pairing orally. The related and unrelated word tests were conducted three times each. A previous study demonstrated that the number of the correct answers for related and unrelated word tests in SP-A was strongly correlated with verbal memory index and verbal paired associates sub-tests of the Wechsler Memory Scale-revised [29]. We calculated and combined the number of correct answers in all testing rounds. The combined correct answers for each test were used in the analysis.

2.3. Magnetic resonance imaging

MRI was performed using a MAGNETOM Advanto 1.5 T scanner (SIEMENS Healthineers, Erlangen, Germany) by radiologic technicians. Axial, coronal, and sagittal T1-weighted spin-echo (SE) images of the whole brain were obtained. For sagittal images, 3D T1-weighted SE images were obtained using the following parameters that were recommended for the VSRAD system: repetition time, 1,600 ms; echo time, 4.0 ms; slice thickness, 1.2 mm; flip angle, 15°; field of view, 230 × 230 mm; matrix, 256 × 256. We then used the VSRAD Advance 2 software (Esai, CO., Tokyo, Japan) to calculate the degree of hippocampal atrophy. The software calculated the mean value of positive Z-scores as the degree of hippocampal atrophy in the targeted volumes of interest by comparing the participants' gray matter concentration voxel-by-voxel with that of the original database template. The equation used was as follows: Z-score = ([control mean] - [individual value]) / (control standard deviation). The acquisition process was followed as previously described [8].

2.4. Statistical analysis

Data about participants' characteristics were presented as mean ± standard deviation (SD) or median (quintile range) for numerical data or in actual numbers for category data. The normality of the obtained data was confirmed using the Shapiro–Wilk test. Correlation analyses were conducted between the mean Z-score from the VSRAD analysis and the mean or median score of each neuropsychological test using Pearson's product-moment correlation coefficient (R) or Spearman's rank correlation coefficient (Rho). Since the results of neuropsychological tests are reported to be influenced by age, sex, and years of education [30,31], Spearman's partial correlation analysis was conducted to control for these variables. All statistical analyses were conducted using SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $p < 0.05$.

3. Results

A total of 15 potential participants were initially included in this study. One participant was excluded as silent ischemia was detected on their brain MRI scan. Another participant's neuropsychological test data were missing. Ultimately, 13 participants were included in the study. The demographic characteristics of the participants are presented in Table 1.

The correlational analyses revealed significant correlations between the VSRAD Z-score and the mean scores on the RCPM ($r = -0.590$, $p = 0.034$), TMT part B ($r = 0.684$, $p = 0.01$), and the median score of the related component of the SP-A (rho = -0.676, $p = 0.011$; Fig. 1). However, there were no significant correlations between the Z-score and TMT part A and the unrelated component of the SP-A. The results of Spearman's partial correlation analysis are presented in Table 2. The correlation became stronger in RCPM and TMT part B by controlling age, sex, and years of education.

4. Discussion

This exploratory retrospective study examined correlations between hippocampal atrophy, evaluated by the VSRAD, and neuropsychological tests in non-demented Japanese older adults. We found significant correlations between the relative level of hippocampal atrophy and TMT part B, RCPM, and SP-A (related) test scores. The correlation in RCPM and TMT part B became stronger after controlling for the effects of age, sex, and years of education. To the best of our knowledge, our study was the first to demonstrate those relationships among non-demented Japanese older adults.

We found TMT part B to be the most strongly correlated with hippocampal atrophy. A previous study revealed a moderate correlation between TMT part B scores and hippocampal volume in elderly individuals from Western countries [12], but no study is available among the Asian population. A previous study revealed that performance on the TMT part B was one of the most precise predictive variables for the progression of MCI to dementia [32]. Another study observed task-related activation in extensive regions of the bilateral frontal, parietal temporal, and occipital lobes while completing the TMT part B; temporal lobe activation also decreased with increasing age [33]. This indicates that TMT part B is a sensitive test that might reflect underlying hippocampal atrophy and may be useful in detecting an early cognitive decline in older adults—including the Japanese population. Contrastingly, TMT part A scores did not correlate with hippocampal atrophy. A previous study revealed that the prevalence of errors increased with age in TMT part B but not part A [34]. It was also revealed that advanced age led to a longer completion time of TMT part B but not part A [31]. These studies may indicate that compared to part B, TMT part A is not sensitive to age—a cause of hippocampal atrophy [10,35].

Table 1
Participant characteristics (n = 13).

Variables	
Age, years	71.2 (±5.2)
Sex (male/female), no	5 / 8
BMI (kg/m^2)	21.8 (±3.4)
Education, years	13.4 (±1.7)
RCPM, points	31.9 (±3.1)
TMT	
Part A, sec	36.9 (±9.4)
Part B, sec	83.5 (±26.8)
S-PA	
Related test, points	28.0 (26.0–29.0)
Unrelated test, points	9.3 (±6.5)
Z-score	0.8 (±0.3)

Data are represented as mean ± standard deviation or median (quintile range).
BMI, body mass index; RCPM, raven's colored progressive matrices test; TMT, trail making test; SP-A, standard verbal paired associates learning test.

The RCPM, one of the most frequently used tests to assess visual-spatial ability, was also moderately correlated with the degree of hippocampal atrophy. No study is available that reveals the relationship between RCPM and hippocampal in people with or without dementia. People with AD sometimes exhibit visual disorders, and a previous study revealed that patients with AD make more errors on the RCPM than healthy elderly individuals [17]. Therefore, the visuospatial function may be an important indicator of hippocampal volume reduction in the elderly. Another study revealed that visuospatial memory, evaluated using the Repeated Battery for the Assessment of Neuropsychological Status, was correlated with hippocampal volume in older people [13]. These studies may indicate that visuospatial function is related to hippocampal atrophy and thus support our findings. Therefore, the RCPM—a widely known, simple test of cognitive function—could be used as a screening tool to detect brain atrophy.

Furthermore, we found that the related component of the SP-A test was correlated with hippocampal atrophy but not the unrelated component. This result is unsurprising because some prior studies have observed correlations between verbal memory functions and hippocampal volume in non-demented elderly individuals [11,12]. Additionally, the SP-A is a widely used verbal memory test in Japan and should thus be further investigated in the context of detecting hippocampal atrophy. However, it is unclear why the unrelated component of the test was not correlated to the VSRAD Z-scores. A previous study revealed increased hippocampal activity when viewing high-imagery word pairs compared to low-imagery word pairs [36]. Our result may also be caused by increased hippocampal activation when hearing related word pairs, which can be imaged more easily than hearing unrelated word pairs.

Although the MMSE is a widespread screening tool for cognitive function, other neuropsychological tests, especially the TMT part B, might be used to screen for brain health or to detect older individuals at increased risk of hippocampal atrophy. Performance on the RCPM and related SP-A test might also be predictive of hippocampal volume changes in non-demented elderly individuals. Our results could contribute to the development of methods to predict hippocampal atrophy prior to cognitive decline in the older Japanese population.

This study had some limitations. First, the sample size was small. However, despite this, there were moderate to strong correlations between the degree of hippocampal atrophy and the different neuropsychological test scores. A larger sample size study that utilizes multiple regression analysis to predict the degree of hippocampal atrophy should be conducted in the future. Second, because the VSRAD database was obtained from Japanese participants only, our results might not be applicable to people from other ethnicities. Therefore, these results should be interpreted carefully.

5. Conclusion

We found a strong correlation between hippocampal atrophy and test scores on the TMT part B, and moderate correlations with the RCPM and SP-A related tests after controlling for age, sex, and years of education in Japanese non-demented older adults. These neuropsychological tests, especially the TMT part B, might be useful for assessing and detecting hippocampal atrophy in non-demented Japanese elderly individuals and should be studied further to develop potential screening methods to detect brain atrophy.

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CRediT authorship contribution statement

Keita Sue: Conceptualization, Writing – original draft. **Hajime**

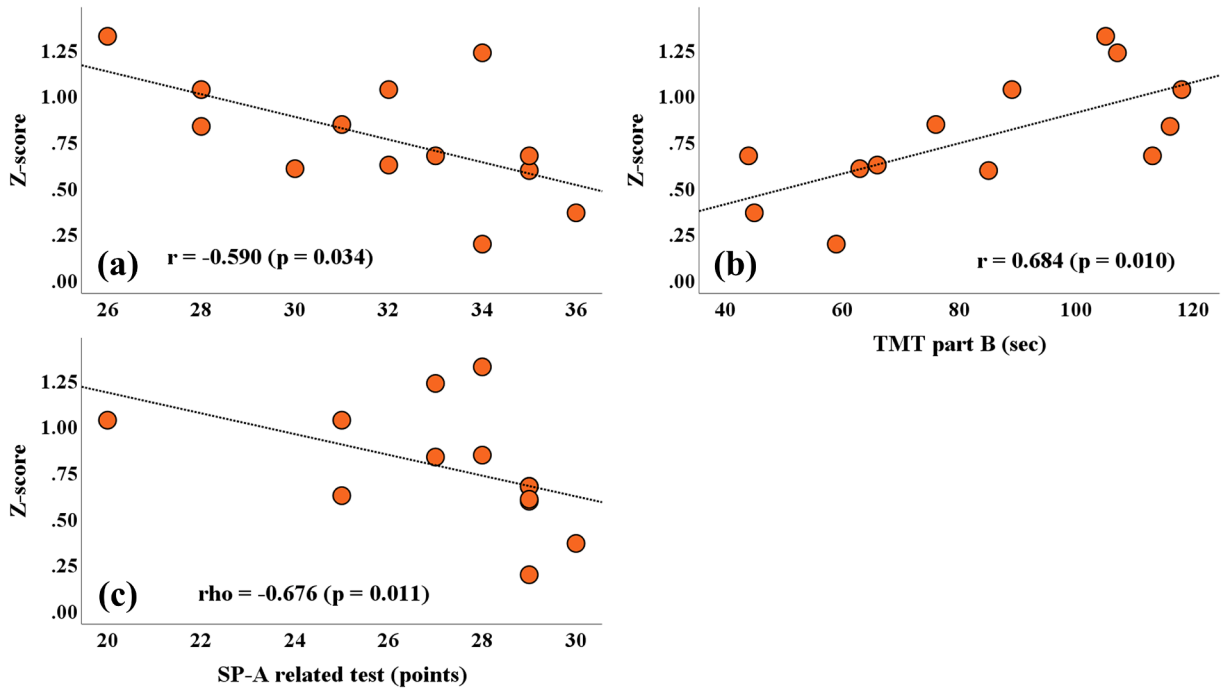

Fig. 1. Correlations between neuropsychological tests and hippocampal atrophy. (a) Raven's Colored Progressive Matrices test; (b) Trail Making Test part B; (c) the related component of the Standard Verbal Paired Associate Learning Test.

Table 2
Correlations between Z-scores and neuropsychological tests controlled for age, sex, and years of education.

	RCPM	TMT part B	SP-A related test
Z-score	−0.691 (p = 0.027)	0.823 (p = 0.003)	−0.663 (p = 0.027)

RCPM, raven's colored progressive matrices test; TMT, trail making test; SP-A, standard verbal paired associate learning test.

Hirabayashi: Data curation, Writing – review & editing. **Michihiko Osawa:** Data curation. **Taiki Komatsu:** Conceptualization, Supervision.

Declaration of Competing Interest

The authors 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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