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ORIGINAL ARTICLE

Cognitive decline and slower reaction time in elderly individuals with mild cognitive impairment

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Abstract

Aim: The relationship between declining performance, as measured by changes in reaction time, and declining cognitive function has not been critically studied. The aim of the present study was to investigate the association between reaction time during a task and cognitive ability in elderly Taiwanese individuals.

Methods: Patients aged 65 years or older with mild cognitive impairment (MCI) (n = 33) and Alzheimer's disease (n = 26) were recruited from the neurology clinic of a regional hospital in southern Taiwan. In addition, 28 healthy controls aged 65 years or older were recruited from the community. The cognitive performance of the study participants was assessed using the Cognitive Abilities Screening Instrument (CASI). A computer-administered simple reaction time (SRT) task and a flanker reaction time (FRT) task were administered to assess participants' cognitive function. A non-parametric Kruskal–Wallis test was performed to compare CASI scores, SRT, and FRT among the three groups. ANOVA was also used to compare CASI scores, inverse-transformed SRT, and inverse-transformed FRT among the three groups, with adjustment for age and years of education. Additionally, Pearson's partial correlation coefficients were used to assess the association of CASI scores with inverse-transformed SRT, and inverse-transformed FRT within each of the three groups.

Results: Significant differences in CASI scores, SRT, and FRT were found between the Alzheimer's disease group and the other two groups, either with or without adjustment for age or education. The reaction time of patients with Alzheimer's disease was significantly slower than the other two groups. Moreover, significant correlation between CASI and FRT was found in patients with MCI.

Conclusion: Altered performance in a speed task was observed in patients with MCI. The FRT task should further be explored for its role as a marker for cognitive decline in elderly individuals, particularly in those with MCI.

Key words: *Alzheimer's disease, cognitive function, mild cognitive impairment, psychological techniques, reaction time.*

INTRODUCTION

Cognitive decline associated with mild cognitive impairment (MCI) and Alzheimer's disease (AD) is a prevalent dysfunction among elderly individuals.[1] Patients' quality of life can be seriously impaired due to medical and financial burden.[2] Several instruments have been developed to measure cognitive function,[3,4] and among them, the Cognitive Abilities Screening Instrument (CASI) is commonly used in dementia research and clinical practice in Asia as well as other areas.[5–8] The CASI was developed for use in geriatric populations based on the items in the Hasegawa Dementia Scale,[9] the Mini-Mental State Examination (MMSE),[10] and the Modified Mini-Mental State Test.[11] Therefore, subsets of the results from the CASI can be compared with existing or future literature that involves the use of the Hasegawa Dementia Scale, the MMSE, or the Modified Mini-Mental State

Test. The CASI can provide quantitative assessment on different domains of cognitive ability, including attention, concentration, orientation, short-term memory, long-term memory, language abilities, visual construction, list-generating fluency, abstraction, and judgement. It was also found to be a reliable cross-cultural measure of cognitive impairment.[5] A study of 1501 adults aged 65 years or older in northern Japan indicated that the CASI score differed between subjects with MCI and those with AD.[12] Another study of 475 Taiwanese patients with AD showed that CASI was able to distinguish different levels of dementia.[13] A study of 807 adults aged 55–100 years in China showed that the Chinese version of CASI has excellent test–retest reliability ($r = 0.97$, $P < 0.001$) and has better sensitivity (94.5%) and specificity (89.5%) for screening of dementia than the MMSE (92.7% and 85.1%, respectively).[14]

Reaction time (RT) in behavioural tasks is considered a marker of cognitive function because RT is associated with neural functioning. Altered RT was found to be associated with diminished white matter in brain areas related to visuospatial cognition,[15] and a relationship between white matter disorders and dementia has also been identified.[16] It was found that increased functional connectivity and activation of the hippocampus is associated with shorter RT.[17] A functional magnetic resonance imaging study confirmed that increasing functional connectivity in multiple areas, across the somatomotor, orbitofrontal, and subcortical networks, was related to a faster RT during a visual search task.[18] It was also found that RT was slower in patients with MCI and AD.[19,20] In addition, measuring RT is a non-invasive procedure that can readily be administered to study participants in clinical settings. To study executive functions, such as response inhibition and selective attention, flanker RT (FRT) is often used.[21] FRT has a higher cognitive loading than a simple RT (SRT), and FRT scores have been shown to be associated with neurodegenerative disease and dementia.[22,23] Although CASI scores have been found to be associated with dementia, the association between CASI and RT is unclear, particularly in patients with MCI. Therefore, the aim of the present study was to examine the association between RT (both SRT and FRT) performance and cognitive ability (as measured by CASI scores) among individuals with ongoing cognitive decline. We hypothesized the following: (i) patients with AD would have a poor CASI performance and lower FRT than healthy controls and those with MCI; (ii) patients with MCI would have an RT performance level between those with AD and healthy controls; and (iii) CASI scores and RT would be associated within each of the three groups.

METHODS

Study participants

Patients aged 65 years or older with cognitive decline (MCI and AD) were recruited from the neurology clinic of the Dalin Tzu Chi Hospital in southern Taiwan. In this study, patients were defined as having MCI if they met the following criteria: (i) had an MMSE score above a cut-off point of 25 for the literate and 14 for the illiterate;[24] and (ii) had a Clinical Dementia Rating (CDR) of 0.5 as assessed by neurologists.[25,26] Patients were defined as having AD if they met the clinical criteria for Alzheimer's-type dementia according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, and had a CDR score of 1. In addition, healthy controls aged 65 years or older were recruited from the community through an advertisement. These individuals had none of the conditions listed in the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for Alzheimer's-type dementia and had a CDR score of 0 as well as an MMSE score within the normal range.

The exclusion criteria for this study included having uncorrected vision or a hearing deficit, as well as the presence or a history of alcoholism, severe psychiatric disorder, significant cerebrovascular disorder, neurological disorder, intellectual deficiency, or any systemic diseases known to impair cognition.

The protocol of this study was approved by the Institutional Review Board of the Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (No. B10401004). The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from patients and their family caregivers.

Cognitive ability assessment

Study participants' cognitive performance was assessed by the CASI. The CASI can provide quantitative assessment of different cognitive domains, including attention, concentration, orientation, short-term memory, long-term memory, language abilities, visual construction, list-generating fluency, abstraction, and judgement. In the present study, a validated Chinese version of the CASI with 20 items was used.[27] The total scores range from 0 to 100, with higher scores indicating better cognitive performance.

Reaction time assessment tool

Computer-administered SRT and FRT tasks (E-Prime software, version 1.1; Psychology Software Tools, Inc., Sharpsburg, PA, USA) (http://www.pstnet.com) were used to assess participants' reaction time. In the test, study participants were asked to indicate the direction of a centrally presented arrow as quickly and accurately as possible (Fig. 1). The SRT task required the participants to identify the direction (left of right) of the centre arrow between two crosses by pressing the corresponding directional key on a computer keyboard. For the FRT task, the display showed two flanking arrows on either side of the central arrow. The purpose of the flanking arrows was to serve as distracting non-target stimuli for the test. Participants were instructed to identify the direction of the centre arrow by pressing the corresponding directional key on a computer keyboard while ignoring the flanking arrows.[21] Both the SRT and FRT tasks had a total of 80 sets of stimuli that were presented in a random order on the computer display. Each stimulus was presented on the computer display for 1 s. The RT of the 80 stimuli for the SRT and FRT task were averaged to form a mean SRT and a mean FRT for each participant to be used in subsequent analyses.

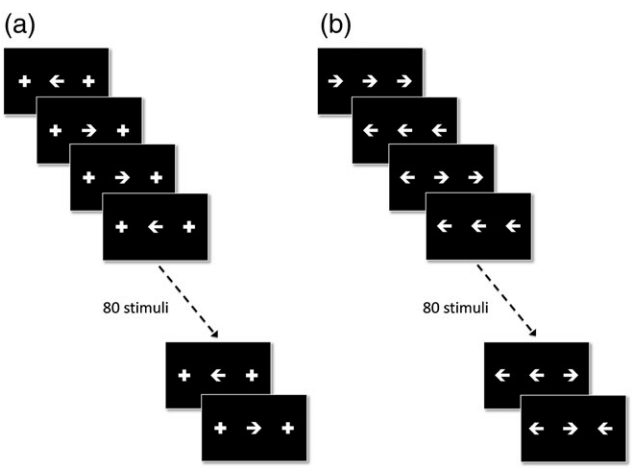

Figure 1 Schematic representation of the simple and flanker reaction time tasks. (a) For the simple reaction time task, each study participant was asked to identify the direction of the centre arrow between two crosses by pressing the button on a computer keyboard corresponding to the direction of the centre arrow (left or right). A total of 80 stimuli were presented to each participant. (b) For the flanker reaction time task, the display showed two flanking arrows on either side of the central arrow. Participants were again instructed to identify the direction of the centre arrow by pressing the button on a computer keyboard corresponding to the direction of the centre arrow (left or right) while ignoring the flanking arrows.

Statistical analysis

A non-parametric Kruskal–Wallis test was performed for continuous variables to test the overall group differences. When the overall comparison was significant, post-hoc pairwise comparisons were performed with Bonferroni correction. For the categorical variable sex, a χ^2 test was used to compare the distribution among the three groups. Because the distributions of SRT and FRT were positively skewed, the data were transformed inversely. To control for the potential confounding effects of age and education, ANOVA was conducted to compare the inverse-transformed SRT and FRT between the three groups. In addition, correlations of CASI scores with inverse-transformed SRT and FRT were calculated using Pearson's partial correlation coefficients, controlling for age and years of education. The threshold for statistical significance was set at 0.05. All statistical analyses were conducted using SPSS version 24.0 for Windows, (IBM Corp., Armonk, NY, USA).

RESULTS

In total, 87 participants (28 controls, 33 MCI, and 26 AD) were enrolled in the study. The demographic and clinical characteristics are shown in Table 1. The AD group was significantly older than the MCI and control groups ($P = 0.002$). The AD group also had fewer years of education, but the differences were not statistically significant ($P = 0.064$).

There were significant differences between CASI scores among the three groups. Pairwise comparison with Bonferroni correction indicated that the score of

Table 1 Characteristics of controls and participants with MCI or AD

Variable	Control (n = 28)	MCI (n = 33)	AD (n = 26)	P-value			
				Overall	Control vs MCI	Control vs AD	MCI vs AD
Age (years)	73.7 ± 5.4 [73.5]	74.9 ± 5.6 [75.0]	79.5 ± 6.1 [80.0]	0.002	>0.999	0.002	0.020
Sex, *n* (%)				0.585	—	—	—
Male	12 (42.9)	10 (30.3)	10 (38.5)				
Female	16 (57.1)	23 (69.7)	16 (61.5)				
Education (years)	7.7 ± 5.0 [6]	5.6 ± 4.0 [6]	4.9 ± 3.9 [6]	0.064	—	—	—
CASI score	89.0 ± 8.2 [90]	78.4 ± 12.0 [82]	51.5 ± 15.9 [54]	<0.001	<0.001	<0.001	0.009
Adjusted CASI score†	85.9 ± 10.1	79.2 ± 9.9	54.0 ± 10.3	<0.001	0.032	<0.001	<0.001
SRT (s)	769.2 ± 269.8 [654.2]	922.1 ± 329.3 [852.9]	1538.4 ± 1055.9 [1208.4]	<0.001	0.203	<0.001	0.018
FRT (s)	907.1 ± 364.7 [720.8]	1053.0 ± 393.5 [961.3]	2664.6 ± 2623.3 [1852.8]	<0.001	0.308	<0.001	<0.001
InvSRT	14.32 ± 4.06 [15.31]	12.21 ± 4.14 [11.72]	8.67 ± 4.18 [8.28]	<0.001	0.203	<0.001	0.018
InvFTR	12.34 ± 3.54 [13.87]	10.65 ± 3.40 [10.40]	5.94 ± 3.32 [5.40]	<0.001	0.308	<0.001	<0.001
Adjusted invSRT†	13.68 ± 3.97	12.40 ± 3.87	9.11 ± 4.06	<0.001	0.624	<0.001	0.008
Adjusted invFRT†	11.90 ± 3.33	10.84 ± 3.24	6.18 ± 2.28	<0.001	0.637	<0.001	<0.001

† ANOVA was performed to adjust for the potential confounding effects of education and age on CASI score, invSRT, and invFRT. Values shown are least square mean ± SD of education = 6.05 years and age = 75.89 years.

AD, Alzheimer's disease; CASI, the Cognitive Abilities Screening Instrument; FRT, flanker reaction time; InvFTR, 10 000/FRT; InvSRT, 10 000/SRT; MCI, mild cognitive impairment; SRT, simple reaction time. Values are mean ± SD and [median] except otherwise indicated. Overall P-values for continuous variables were obtained by Kruskal–Wallis test except for adjusted invSRT and adjusted invFRT. When the overall comparison was significant, post-hoc pairwise comparisons were performed. Overall P-values for sex were obtained by χ^2 test. All P-values for pairwise comparisons shown were already adjusted by Bonferroni correction.

the AD group was significantly lower than those of the MCI group ($P < 0.001$) and the controls ($P = 0.009$). In addition, the score of the MCI group was significantly lower than that of the controls ($P < 0.001$). Similar results were observed when CASI scores were adjusted for age and years of education using ANCOVA.

For the non-transformed RT, the SRT of the AD group was significantly longer than those of the MCI ($P = 0.018$) and the controls ($P < 0.001$), but the SRT of the MCI group did not differ from that of the controls ($P = 0.203$). Similarly, the FRT of the AD group was significantly longer than those of the MCI ($P < 0.001$) and the controls ($P < 0.001$), but the FRT of the MCI group did not differ from that of the controls ($P = 0.308$). When the inverse-transformed SRT and FRT were adjusted for age and years of education, the results were similar. The inverse-transformed SRT and FRT of the AD group were significantly shorter than those of the MCI group ($P = 0.008$ and $P < 0.001$, respectively) and controls ($P < 0.001$), but those of the MCI group did not differ from those of the controls ($P = 0.624$ and $P = 0.637$, respectively).

Table 2 Correlation analysis of CASI score with simple reaction time and flanker reaction time

		Control	MCI	AD
CASI and invSRT	r	0.027	0.334	0.174
	P-value	0.897	0.066	0.416
CASI and invFRT	r	0.037	0.422	0.105
	P-value	0.858	0.018	0.624

AD, Alzheimer's disease; CASI, Cognitive Abilities Screening Instrument; invFTR, 10 000/franker reaction time; invSRT, 10 000/simple reaction time; MCI, mild cognitive impairment; r, Pearson's partial correlation coefficient adjusted for age and years of education.

To evaluate the correlations between CASI scores and RT adjusted for age and years of education, Pearson's partial correlation coefficients were separately calculated for the control, MCI, and AD groups (Table 2). In both the control and AD groups, no significant correlations were observed either between CASI scores and inverse-transformed SRT or between CASI scores and inverse-transformed FRT. In the MCI group, a significant correlation was found only between CASI scores and inverse-transformed FRT (partial $r = 0.42$, $P = 0.018$). In other words, a better cognitive performance was associated with a shorter FRT. Figure 2 shows scatterplots of CASI

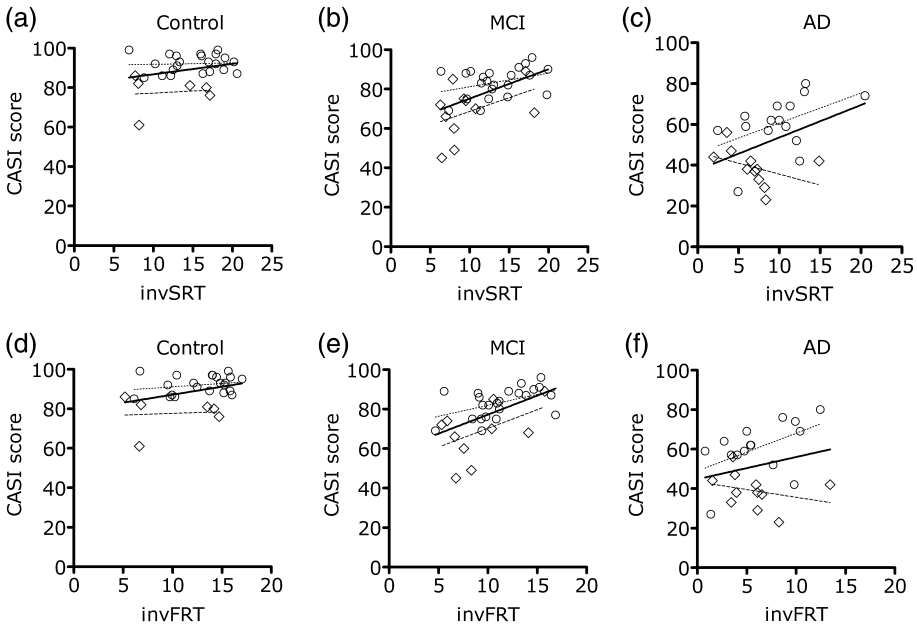

Figure 2 Scatterplots of CASI scores versus inverse-transformed simple reaction time (a-c) and inverse-transformed flanker reaction time (d-f) for controls, patients with mild cognitive impairment, and patients with Alzheimer's disease. Three separate linear regression lines are shown in each graph for all patients (solid line), patients with <6 years of education (dash line), and patients with ≥6 years of education (dotted line). ○, ≥6 years of education; ◇, <6 years of education; AD, Alzheimer's disease; CASI, the Cognitive Abilities Screening Instrument; invFRT, 10 000/flanker reaction time; invSRT, 10 000/simple reaction time; MCI, mild cognitive impairment.

scores and inverse-transformed SRT and FRT for controls, MCI, and AD, with separate linear regression lines for all patients, patients with at least 6 years of education, and those with fewer than 6 years of education.

DISCUSSION

Our findings indicated that AD was accompanied by significantly poor performance on the SRT and FRT tasks; patients with MCI showed a similar performance compared with controls. The three groups had significantly different CASI scores. In addition, a significant association between CASI score and FRT was found in patients with MCI. These findings were robust after adjustment for age and years of education.

The differences found in CASI scores add to the findings of Liu *et al.* and Meguro *et al.* and further support the validity of the CASI.[12,13] Our results indicate that patients with AD have significantly slower RT than the controls, and this is in agreement with previous findings.[20] Several studies have confirmed altered structure and function of the prefrontal or hippocampus in patients with AD,[28–32] which may be associated with slower RT.[17,18]

Our study also found no significant difference in RT between MCI individuals and controls, which is consistent with the results of a study that included 16 healthy controls, 15 MCI, and 7 AD.[33] Conversely, another study comparing 172 patients with MCI and 79 controls found a significantly longer SRT in MCI patients, which could be attributed to the larger sample size used and the difference in the mean age of the participants.[19] Further studies are required to clarify this discrepancy.

The significant correlation ($r = 0.42$, $P = 0.018$) found between CASI scores and FRT in the MCI group, but not in the control or AD group, suggested that the FRT task may be used as a tool for assessing the severity of cognitive decline in patients with MCI (Fig. 2b,e). In addition, previous studies indicated that a certain proportion (8–39%) of individuals with MCI may progress to AD within 1 year,[34–37] whereas 2–53% of them can revert back to normal cognitive level.[37–39] It is plausible that patients with a slower FRT might have a higher risk of developing AD, whereas those with a faster FRT might not. Further longitudinal follow-up studies are warranted to investigate the predictive value of FRT with regard to the development of AD in patients with MCI.

In the control group, the lack of correlation between CASI scores and either inverse-transformed SRT or inverse-transformed FRT could be attributed to a ceiling effect in the CASI, where most participants scored well on the CASI (Fig. 2a,d). Conversely, in the AD group, the lack of correlation did not appear due to a floor effect of the CASI. In Figure 2c,f, the slopes of the linear regression lines are in opposite directions for patients with at least

6 years of education and those with fewer years. This suggests education level may be an effect modifier on the association between CASI scores and inverse-transformed RT. Additional studies with a large sample size are needed to understand if and how CASI scores are associated with RT in AD patients with different levels of education.

Several limitations to this study should be mentioned. Firstly, the statistical power is limited because of the relatively small sample size. Nevertheless, significant differences in CASI scores and RT between controls and AD as well as between MCI and AD were observed. Secondly, CASI was used as a proxy for global cognitive function, and our findings may not be generalizable to other markers of global cognitive function. Thirdly, we used the MMSE and CDR for the diagnosis of MCI, which is routine in Taiwan.[40] The possibility of false-positives and false-negatives in MCI and controls cannot be fully ruled out.

In summary, our findings address the importance of global cognitive function assessment and performance tasks for cognitive decline. The FRT task may be a useful tool for assessing the severity of cognitive decline in patients with MCI. Moreover, it may be worth exploring the utility of the FRT task as a screening tool for MCI because early interventions, such as cognitive training, may improve cognition during the early stages of cognitive decline in older adults.[41]

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