Original Research Article

Set-Shifting Ability Is Associated with Gray Matter Volume in Older People with Mild Cognitive Impairment

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Key Words

Gray matter · Executive functioning · Mild cognitive impairment

Abstract

Background/Aims: An understanding of the association between gray matter volume and executive functioning could provide strategies to reduce dementia risk in older people with mild cognitive impairment (MCI). **Methods:** In a cross-sectional analysis, we assessed executive functioning in 83 older people with MCI using three standard neuropsychological tests: set shifting (difference between Trail Making Test Parts B and A), working memory (difference between Digit Span forward and backward from the Wechsler Adult Intelligence Scale-IV), and selective attention/response inhibition (difference between the second and third conditions of the color- and picture-word Stroop test). Gray matter volume was computed from brain MRIs and SIENAX from FSL software. **Results:** Gray matter volume was significantly associated with set-shifting performance after accounting for age, gender, body mass index, education, and global cognition (standardized $\beta = -0.376$, $p = 0.001$), but not with working memory or selective attention/response inhibition. **Conclusion:** The executive function of set-shifting ability was correlated with gray matter volume in older people with MCI.

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Introduction

Many older people are at risk of cognitive impairment, one of the most disturbing aspects of aging [1]. When these changes in cognitive function are first clinically recognizable, they are often referred to as mild cognitive impairment (MCI). MCI is considered to be the transitional phase between normal aging and dementia and is recognized as the prodromal stage

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of Alzheimer's disease (AD) [2]. Thus, MCI is a putative target for the prevention of neurodegenerative disease [2, 3]. The identification of individuals with MCI who will progress to AD is a critical issue.

Older people experience a significant degree of brain volume loss across the life span. Longitudinal studies have reported that brain volume decreases by 0.2–0.5% each year [4–7]. Among older people experiencing cognitive decline such as MCI, the rate of brain volume loss (notably gray matter volume loss) is higher than that among healthy older people [8–10]. Numerous studies have demonstrated that MCI-related regional gray matter volume loss is most significant in the medial temporal and frontal cortex, including the prefrontal cortex [11–13]. Assessment of gray matter volume may allow early detection of MCI and subsequent neurodegenerative disease.

Scanning MRIs are not suitable as primary clinical screening to assess gray matter volume since they require money and time, and the assessment of cognitive functioning using neuropsychological tests is more useful in clinical settings. It is well known that the prefrontal cortex plays a crucial role in cognitive functioning and executive functioning in particular [14]. Further, there is substantial evidence that different areas of the prefrontal cortex exert different roles in executive control [15, 16]. However, the association between gray matter volume and cognitive dysfunction in patients with MCI remains unclear.

An understanding of the association between gray matter volume and executive functioning could provide strategies to reduce dementia risk in high-risk populations. The present study examined associations between cognitive performance, specifically executive functioning, and gray matter volume in older people with MCI.

Methods

Participants

The sample for this cross-sectional study consisted of 83 community-dwelling older people with MCI (mean age 75.4 years; 49.4% females) who consented and completed the baseline assessment of a randomized controlled trial (RCT; trial registration UMIN-CTR UMIN000003662) evaluating the effects of multicomponent exercise on cognitive functioning. The Ethics Committee of the National Center for Geriatrics and Gerontology approved the study protocol. The study design and primary results of the RCT have been described previously [17]. All participants gave their written informed consent prior to study participation. Participants enrolled in the RCT were aged 65 years and over, community dwelling, and not suffering from dementia. All participants met the Petersen criteria for MCI [2]. Participants who had either a Clinical Dementia Rating of 0; a Clinical Dementia Rating of 1–3 along with a history of neurological, psychiatric, or cardiac disorders, or other severe health issues; used donepezil; showed impairment in basic activities of daily living; or participated in other research projects were excluded from the RCT study. A total of 100 subjects participated in the RCT and completed baseline neuropsychological assessments. In the present cross-sectional imaging analysis, 17 participants were excluded owing to poor-quality MRI scanning data.

Dependent Variable: Gray Matter Volume Measured with MRI

MRIs were performed with a 1.5-tesla system (Magnetom Avanto, Siemens, Germany). Three-dimensional volumetric acquisition with a T1-weighted gradient echo sequence was then used to produce a gapless series of thin sagittal sections using a magnetization preparation, rapid-acquisition gradient-echo sequence (repetition time, 1,700 ms; echo time, 4.0 ms; flip angle, 15°; acquisition matrix, 256 × 256, and 1.3-mm slice thickness). Brain tissue

volume, normalized for subject head size, was estimated with SIENAX [18, 19], which is part of FSL (FMRIB Software Library, version 5.0) [20]. SIENAX first extracted brain and skull images from the single whole-head input data [21]. The brain image was then affine-registered to MNI152 space [22, 23] (using the skull image to determine the registration scaling); this was done primarily in order to obtain the volumetric scaling factor to be used in normalizing head size. Next, tissue type segmentation with partial volume estimation was completed [24] in order to calculate the total volume of brain tissue (including separate estimates for the volume of gray matter, white matter, peripheral gray matter, and ventricular cerebrospinal fluid).

Independent Variables

Demographic Data

We interviewed all participants about their age, gender, body mass index (BMI), and education. In addition, the Timed Up and Go (TUG) test was used as a mobility assessment [25]. The TUG test involves the participant rising from a standard armchair, walking a distance of 3 m at a normal and safe pace, turning around, walking back to the chair, and sitting down again. TUG is measured in seconds using a stopwatch. The time taken to complete the TUG test was measured twice, and the best-timed trial was used for each participant's score.

Global Cognition

Global cognition was assessed using the Mini-Mental State Examination (MMSE) administered by licensed and well-trained clinical speech therapists. The MMSE consisted of 11 tasks including the assessment of memory, comprehension, orientation to time and place, praxis, and attention [26]. Lower scores on the MMSE indicated greater severity of cognitive impairment.

Cognitive Performance: Executive Functioning

We referred to previous studies for the standard assessments of executive functioning [27, 28]. We assessed three key executive functions, including (1) set shifting; (2) working memory, and (3) selective attention and conflict resolution. These measures are distinct, but moderately correlate with one another.

Set Shifting

The Trail Making Test (TMT, Parts A and B) [29] was used to assess set shifting. In TMT Part A, participants are asked to draw lines to connect 25 circles numbered from 1 to 25 as quickly as possible. In TMT Part B, participants are asked to connect circles containing numbers (from 1 to 13) or letters (from A to L) in an alternating numeric, alphabetical order (1-A-2-B-3-C-...-13-L). Errors must be corrected immediately and the sequence reestablished. In the Japanese version of TMT Part B, letters from the Roman alphabet were exchanged for kana characters. The amount of time (in seconds) it took to complete each task was recorded. We calculated the time difference between Parts B and A to index set shifting. A smaller time difference indicated better set shifting (Δ TMT) [30].

Working Memory

We administered forward and backward Digit Span tests from the Wechsler Adult Intelligence Scale-IV in order to assess working memory. Both conditions required participants to repeat sequences of verbally presented digits of increasing length (in either forward or backward order) [31]. The examiner pronounces a list of digits at a rate of approximately one digit per second, and subjects are required to immediately repeat the list in the same order. If they succeed, a list one digit longer is presented. If they fail, a second list of the same length

Table 1. Characteristics of participants

Variable at baseline	Total (n = 83)	Range (min. to max.)
Age, years	75.4±6.8	65 to 93
Males, n (%)	42 (50.6)	–
BMI	22.8±3.2	16.9 to 30.7
Education, years	10.7±2.6	6 to 17
MMSE score	26.6±2.5	17 to 30
TUG, s	8.9±2.0	5.9 to 16.1
ΔTMT, s	74.5±98.3	–74 to 562
ΔDS score	2.4±2.1	–3 to 8
ΔStroop score	21.8±21.1	–7 to 148
Gray matter volume, ×10 ⁵ mm ³	7.28±4.00	6.32 to 8.08

DS = Digit Span.

is presented. If subjects are successful on the second list, a list one digit longer is given, as before. However, if subjects also fail on the second list, the test is ended. The length of the digit sequences gradually increases, starting with a sequence of three numbers (e.g., 5, 8, 2) to a sequence of maximum 9 items (e.g., 7, 1, 3, 9, 4, 2, 5, 6, 8). The span is established as the length of the longest list recalled correctly. The same procedure is used for the Digit Span backward task, except that in this case, subjects have to reproduce the sequence of digits in the reverse order and the longest list consists of 8 items. The difference between the forward and backward scores was used as an index of the central executive component of working memory (ΔDS). A smaller score difference indicated better working memory [30].

Selective Attention and Conflict Resolution

We used the color- and picture-word Stroop test to assess selective attention and conflict resolution [32]. There were three conditions. First, participants were instructed to read words printed in black ink out loud (e.g., BLUE). Second, they were instructed to state the color of colored Xs. Finally, they were shown a page with color words printed in incongruently colored ink (e.g., the word 'BLUE' printed in red ink). Participants were asked to name the color in which the words were printed (while ignoring the word itself). We recorded the time participants took to complete each condition. The ability to selectively attend and control response output was calculated as the time difference between the third and the second condition. A smaller time difference indicated better selective attention and conflict resolution (ΔStroop) [30].

Statistical Analysis

Pearson's correlation coefficients were used to quantify the bivariate associations between gray matter volume and age, BMI, education level, mobility, global cognition, and executive functions. Multiple linear regression models were constructed to determine the independent association between executive functioning and gray matter volume. Covariates included in the first model were age, gender, BMI, education, and global cognition (MMSE). The executive functioning variable(s) that were significantly related to gray matter volume in the results of Pearson's correlation coefficients were then entered into the second model. We calculated the R² and standardized β-value for each regression model. The statistical analyses were completed using SPSS for Windows version 17.0 (SPSS, Chicago, Ill., USA). The level of statistical significance was set at 0.05 for all analyses.

Results

Table 1 presents participant characteristics in this study. The results of the correlation coefficient matrix for gray matter volume are given in figure 1. Gray matter volume showed a significantly negative correlation with age ($r = -0.348$, $p = 0.001$). We found a modest but statistically significant negative correlation with set-shifting performance ($r = -0.414$, $p < 0.001$). Worse performance (larger Δ TMT) predicted less gray matter volume.

In the multiple linear regression analyses (table 2), after accounting for covariates including age, gender, BMI, education, and MMSE, set-shifting performance (Δ TMT) was independently associated with gray matter volume (standardized $\beta = -0.376$, $p = 0.001$). The final model accounted for 26% of variance.

Discussion

Gray matter volume correlated significantly with set-shifting ability (less gray matter was associated with worse performance). However, we did not find significant correlations with working memory or selective attention and conflict resolution in older people with MCI. Set shifting requires high-level cognitive ability that includes shifting attention or response patterns based on different rules. Performance on set-shifting tests (such as the TMT) has been shown to be impaired in patients with frontal lobe lesions [33–38], frontal lobe epilepsy [39], frontal-striatal dysfunction due to basal ganglia lesions [34], Parkinson's disease [36], and Huntington's disease [40]. Spulber et al. [9] reported that older people with MCI and greater annualized atrophy (e.g., $>3\%$ per year) were at much higher risk of AD. Thus, brain volume, including gray matter volume, may be a viable sign identifying the risk of progression to AD in older people with MCI. In primary health care settings, we recommend set-shifting assessment to reflect gray matter volume; this assessment may be useful in predicting the risk of dementia in aging populations.

Higher levels of cognitive functioning such as set shifting could be mediated by a predominantly frontal neural network. Set shifting not only relies on brain regions important for cognitive control, but also on brain regions that mediate other fundamental skills critical to good performance, such as visual scanning or motor speed [41]. In the present study, we used TMT to assess the set-shifting ability among older people with MCI. Previously, TMT has been useful to assess not only set shifting, but also to discriminate individuals destined to convert from MCI to AD. Ewers et al. [42] indicated that the AD conversion prediction accuracy of TMT Part B reached 64.6% in a longitudinal study. In addition, Carlson et al. [43] reported that the decline in executive functioning (TMT scores) preceded memory declines associated with progression to AD. According to these previous studies and our findings, TMT to assess set-shifting ability may help in the early detection of those patients with progression to AD.

Several study limitations should be mentioned when interpreting the findings and discussing their implications. First, our analysis was based on a cross-sectional design. We were therefore unable to investigate causal relationships between gray matter volume and executive functioning. Second, we analyzed the gross volume of gray matter rather than a region of interest. Cognitive functions (including executive functioning) are typically defined by functional localization; thus, it will be important to further clarify the association between specific cognitive functions and regions of interest in the brain. Third, this study did not include healthy individuals or patients with dementia. Therefore, additional studies including participants with varying cognitive health will be needed to clarify the relationship between gray matter volume and executive functioning and to characterize dementia-related pathology. Finally, we did not investigate the association between gray matter volume and executive

Fig. 1. Correlation between gray matter volume and the variables analyzed. n.s. = Not significant.

Table 2. Multiple linear regression summary for gray matter volume (n = 83)

Independent variables	R ²	Unstandardized β (standard error)	Standardized β	p value
Model 1	0.145			
Age		-2,164.063 (659.797)	-0.371	0.002
Sex		-8,042.865 (8,609.322)	-0.102	0.353
BMI		891.360 (1,342.780)	0.071	0.509
Education		-1,953.525 (1,795.051)	-0.130	0.280
MMSE		557.854 (1,795.051)	0.036	0.760
Model 2	0.260			
Age		-1,781.855 (627.786)	-0.305	0.006
Sex		-6,941.838 (8,068.405)	-0.088	0.392
BMI		28.461 (1,282.249)	0.002	0.982
Education		-2,038.242 (1,681.123)	-0.136	0.229
MMSE		-1,188.668 (1,776.192)	-0.076	0.505
Δ TMT		-151.373 (44.050)	-0.376	0.001
p < 0.05 indicates significance.				

functioning according to MCI subtypes. The degree of decline in cognitive function varies in nature by MCI subtypes (amnesic vs. non-amnesic, and multiple domain vs. single domain). Thus, the association between gray matter volume and executive functioning should be investigated in consideration of MCI subtypes. These limitations should be addressed in future studies involving prospective designs and broad participation.

Conclusion

Our findings suggest that set-shifting performance is positively associated with gray matter volume in older people with MCI. Set-shifting ability could be more strongly associated with age-related structural brain changes compared to other aspects of executive processes, such as working memory and selective attention and conflict resolution. Therefore, we recommend set-shifting assessment to reflect gray matter volume in primary health care settings.

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Disclosure Statement

There are no financial or personal relationships with other people or organizations that may lead to a conflict of interest.

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