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Cognitive dysfunction in elderly females with depressive symptoms

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A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
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Summary

Background: A depressive state is a common symptom in the elderly and often accompanies cognitive impairment. The coexistence of depressive symptoms and cognitive impairment is a serious problem, as it increases adverse outcomes for health, functional status, and mortality. It would thus be of great value to clarify the cognitive dysfunction associated with depressive symptoms. We aimed to identify the cognitive dysfunction, in particular, impairment of the response inhibition component of executive function, associated with depressive symptoms in elderly females using the Simple Color Reaction Test and Modified Stroop Color-Word Test.

Material/Methods: The study group consisted of 35 elderly women. They performed cognitive function task trials for 9 min. Univariate logistic regression analyses were performed to identify factors associated with the prevalence of the depressive state.

Results: Longer reaction time and lower correction rate of response inhibition trials were related to the prevalence of the depressive symptoms.

Conclusions: Impaired function of response inhibition may be a specific feature of the depressive state. Our findings may help clarify the neural mechanisms underlying the depressive state of elderly females.

key words: depressive symptom • elderly • female • response inhibition

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Background

Elderly females are more likely to be depressed than elderly males [1]. The coexistence of a depressive state and cognitive dysfunction is commonly observed [2], and the cognitive impairment that accompanies depressive symptoms are a serious problem, as they can increase adverse outcomes for health, functional status, and mortality in elderly people [3]. Both depressive symptoms and cognitive dysfunction are increasing along with the aging population of most industrialized nations [4]. It would thus be of great value to clarify the mechanisms underlying the depressive state in terms of cognitive dysfunction as well as to develop evaluation and treatment methods for the cognitive impairment that accompanies depressive symptoms among elderly females.

Executive dysfunction is present in a large number of elderly patients with major depression [4–8]. In particular, the response inhibition component of executive function, evaluated using the Stroop Color-Word Test [9], seems to be important for elderly depressed patients, as that component predicts poor treatment response to antidepressant medication [10,11] as well as chronicity of depression in the elderly [8]. Although a close relationship between depression and dysfunction of response inhibition has been identified [5,6,8], this correlation was mostly limited to geriatric patients with clinically treated major depression rather than a clinically untreated general elderly depressive population. In addition, no comparisons with a control task for the Stroop Color-Word Test or adjustment for general cognitive function have been performed. By using the newly developed Simple Color Reaction Test and the Modified Stroop Color-Word Test, we can assess reaction times and correction rates of control and Stroop trials to assess response inhibition function in detail. Similarly, by using multivariate logistic regression analysis adjusted for general cognitive function, a specific association between the depressive state and response inhibition can be evaluated.

The aim of our study was to identify cognitive dysfunction, with a particular focus on impairment of the response inhibition component of executive function, associated with depressive symptoms among general elderly females by using the Simple Color Reaction Test and the Modified Stroop Color-Word Test.

Material and Methods

Participants

Thirty-five elderly females (≥65 years of age) were recruited. Subjects with dementia diagnosed by a medical doctor (M.T.) were excluded. In addition, we excluded current smokers, subjects body weight less than 35 kg, and those with blood hemoglobin level less than 10.5 g/dl. The presence of good health, which was required for participation, was assessed by physical examination, blood chemistry panel (glucose, creatinine, uremic nitrogen, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, and creatine phosphokinase levels), lipid profile (total cholesterol and triacylglycerol levels), and complete blood count. The study protocol was approved by the Ethics Committee of Osaka City University, and all participants provided written informed consent to participate in this study.

Experimental design

For 1 day before the experiment, participants refrained from intense mental and physical activities, consumed a normal diet, and maintained normal sleeping hours. After a visit at 10:00 a.m., questionnaires were distributed to participants and height and body weight were measured to assess body mass index (BMI) in a room at Osaka City University. BMI was calculated as body weight in kilograms divided by height in meters squared. Thereafter, they performed the Mini-Mental State Examination (MMSE) and a cognitive function task. This study was conducted in a quiet temperature- and humidity-controlled environment. Participants were only allowed to drink water during the experiment.

Questionnaires

Paper-and-pencil questionnaires were distributed to participants. The questionnaires completed by each participant dealt with age, depressive symptoms, appetite, sleep, activities, and life itself. The Geriatric Depression Scale-15 (GDS-15) was used to assess the number of depressive symptoms as well as the depressive state. This questionnaire was specifically developed for older subjects and consisted of 15 questions using a two-level (0–1) scale that evaluate the functional and mood-associated symptoms of depression [12–14]. The total score for the 15-item depression scale ranges from 0 to 15, with higher scores indicating a greater number of depressive symptoms. Subjects with a GDS-15 score ≥6 are considered to be in a depressive state [15]. Participants were asked to subjectively rate their levels of appetite on a visual analogue scale (VAS) from 0 (minimum) to 100 (maximum) [16]. Questions about sleep included items about nocturnal sleeping hours, difficulty in initiating sleep (yes [everyday, often, or sometimes] or no), difficulty in maintaining sleep (yes [everyday, often, or sometimes] or no), and early morning awakening (yes [everyday, often, or sometimes] or no); questions about activities included cultural (yes or no) and exercise activities (yes or no); and one question about life asked if the participant found life worth living (yes or no).

MMSE

The MMSE tests general cognitive function, and the total score for the examination ranges from 0 to 30, with higher scores indicating a greater level of general cognitive function [17]. Normal cognitive function was determined as an MMSE score ≥24 [18].

Cognitive function task

The cognitive task presentation consisted of traffic lights (placed on a letter corresponding to blue or red in Japanese) and traffic signs for walkers (right or left) and turns (right or left) shown on a display of a personal computer screen [19]. Participants performed Task A (Simple Color Reaction Test) for 3 min and Task B (Modified Stroop Color-Word Test) for 6 min. In Task A, they were told to press the right button with their right middle finger if the blue traffic light was presented (placed on a letter corresponding to blue in

Japanese) regardless of traffic signs for walkers or turns; if the red traffic light was presented, they were told to press the left button with their right index finger. In Task B, they had to judge whether the target letter presented at the center of a traffic light was blue or red. If the letter meant blue in Japanese, regardless of the color of the traffic light or traffic signs for walkers or turns, they were to press the right button with their right middle finger; otherwise, they were to press the left button with their right index finger. In these tasks, each trial was presented 100 ms after pressing either of the buttons. During the task period, blue or red trials and traffic signs for walkers (right or left) and turns (right or left) were given randomly, and the occurrence of each color and type of sign was equal. In Task B, the Stroop trial (mismatching the color of the traffic light with the letter) and non-Stroop trial (matching the color of the traffic light with the letter) occurred equally. They were instructed to perform the task trials as quickly and as correctly as possible. The result of each cognitive task trial, that is, a correct response or error, was continuously presented on the display of the personal computer. Before they performed the cognitive function task, they practiced for 3 min.

Cognistat

Cognistat (formerly known as the Neurobehavioral Cognitive Status Examination) is widely used to evaluate a variety of cognitive functions [20]. Cognistat is designed to give an independent assessment of ten central cognitive domains, and the following ten corresponding subtests are scored: attention, naming, similarities/verbal abstraction, everyday/concrete judgement, understanding of simple commands, repetition of sentences, visuoconstruction, memory, calculation, and orientation. Correct responses in each subtest are summed, and the test result was presented as a differentiated cognitive profile. If the participant passes the screening test, they are presumed to function normally in that domain, and the tester continues to the next domain. When a participant fails the screening test, it continues with a metric portion that explores a possible deficit further. To results of the Cognistat, we analyzed using a Cognistat Composite Score [21]. Among ten Cognistat subtests, orientation, memory, and naming were performed in order to evaluate cognitive domains other than the executive functions.

Statistical analyses

Differences in mean values between the depressive and non-depressive groups were compared using Student's t-test, and categorical variables were compared using Fisher's exact test. Univariate logistic regression analyses were performed to identify factors associated with the prevalence of the depressive state. All P values were 2-tailed, and P values less than 0.05 were considered statistically significant. Statistical analyses were performed using the SPSS 20.0 software package (SPSS, Chicago, IL).

Results

Characteristics of the depressive and non-depressive groups are shown in Table 1. Among 35 participants, 8 of them (22.9%) showed a depressive state. All participants had MMSE scores ≥24. Although mean age, BMI, and nocturnal sleeping hours, and proportion of difficulty in initiating sleep and difficulty in maintaining sleep did not differ significantly between groups, mean level of appetite was significantly lower, the proportion of early morning awakening sleep was significantly higher, the proportions of cultural activities and finding life worth living were significantly lower, and proportion of exercise activities tended to be lower in the depressive group relative to the non-depressive group. There were no significant differences in mean MMSE scores between two groups. Task A does not involve the Stroop trials; while Task B involves the Stroop trials. In addition, except for the Stroop effect, the two types of the trials are almost similar. Therefore, the reaction time or percent error for the Stroop effect were evaluated as the reaction time or percent error of Task B in the Stroop trials subtracted by those of Task A. Mean reaction times of the Task A, Stroop and non-Stroop trials for the Task B, and Stroop minus non-Stroop trials were significantly longer in the depressive group than the non-depressive group. Although mean correction rates of the Task A and the non-Stroop trials for the Task B did not differ significantly between groups, those of Stroop trials for the Task B and Stroop minus non-Stroop trials were significantly lower in the depressive group relative to the non-depressive group. There were no significant differences in mean orientation, memory, and naming scores between the two groups.

To identify factors associated with the prevalence of the depressive state, univariate logistic regression analyses were performed (Table 2). On univariate logistic regression analyses, early morning awakening (yes *vs.* no) was positively and appetite, cultural activities, and exercise activities (yes *vs.* no), and finding life worth living (yes *vs.* no) were negatively associated with the prevalence of the depressive state. In addition, longer reaction times of the Task A, Stroop and non-Stroop trials for the Task B, and Stroop minus non-Stroop trials were positively associated with the prevalence of the depressive state and lower correction rates of Stroop trials for Task B and Stroop minus non-Stroop trials tended to be positively associated with the prevalence of the depressive state. Orientation, memory, and naming were not associated with the prevalence of the depressive state.

Discussion

These cross-sectional data demonstrate that longer reaction time and lower correction rate of the response inhibition trials were related to the depressive state in elderly females. In addition, awaking in the early morning, appetite loss, not taking part in cultural and exercise activities, and finding life not worth living were associated with the prevalence of a depressive state.

Consistent with previous findings dealing with elderly patients with major depression [5,6,8], dysfunction of response inhibition was observed in our patients. In a prospective cohort study dealing with a general elderly population, dysfunction of the response inhibition evaluated using the Stroop Test was a risk factor for an increased number of the depressed symptoms assessed using GDS-15, although the presence of depressive state was not a risk for cognitive decline [22]. Because 8 of 35 (22.9%) of the general elderly females in this study were in a depressive state (Table 1), knowing about the relationship between the depressive state

Table 1. Baseline characteristics of study participants.

	Non-depressive (n=27)	Depressive (n=8)	*P* value
Age (years)	73.4±4.7	72.9±6.6	0.728
BMI (kg/m^2)	23.8±2.5	23.5±2.6	0.779
Appetite*	80.3±13.7	64.0±21.0	0.017
Nocturnal sleeping hours	6.9±1.0	6.5±1.2	0.333
Difficulty in initiating sleep, yes (%)	15 (55.6)	5 (62.5)	1.000
Difficulty in maintaining sleep, yes (%)	11 (40.7)	6 (75.0)	0.121
Early morning awakening, yes (%)	3 (11.1)	4 (50.0)	0.033
Cultural activities, yes (%)	21 (80.8)	3 (37.5)	0.031
Exercise activities, yes (%)	23 (85.2)	3 (37.5)	0.060
Finding life worth living, yes (%)	25 (92.6)	3 (37.5)	0.003
MMSE score	28.3±1.8	27.5±2.5	0.359
Cognitive task			
Reaction time (sec)			
Task A	0.71±0.19	1.06±0.4	0.004
Task B	0.87±0.19	1.37±0.6	0.001
Stroop trials	0.90±0.21	1.62±1.0	0.001
Non-Stroop trials	0.84±0.18	1.15±0.4	0.003
Stroop minus non-Stroop trials	0.05±0.07	0.47±0.7	0.002
Correction rate (%)			
Task A	99.7±0.4	99.6±0.8	0.693
Task B	96.7±2.2	94.4±5.1	0.087
Stroop trials	94.7±3.6	89.6±10.1	0.037
Non-Stroop trials	98.6±1.2	98.7±2.2	0.895
Stroop minus non-Stroop trials	–3.9±2.9	–9.0±9.8	0.022
Cognistat			
Orientation	9.9±0.4	10.0±0.0	0.587
Memory	7.7±3.1	7.5±3.7	0.953
Naming	9.5±0.8	8.8±1.8	0.115

* Rated on a 100 visual analogue scale from 0 to 100. Data are mean ±SD or number (%).BMI – body mass index; MMSE – Mini-Mental State Examination.

and dysfunction of response inhibition is of value, and might help us develop screening procedures to identify those at high risk of depression as well as to conduct early interventions to achieve a lower incidence of and higher recovery from depression among elderly females.

We found that longer reaction time and lower correction rate of the response inhibition trials were related to the depressive state in elderly females. During the Stroop trials, the color and word dimensions activated the associated responses, resulting in conflict between the activated responses and an increased likelihood of error. This conflict is proposed to activate a conflict monitor in the anterior cingulated cortex (ACC), which in turn engages the control function of the dorsolateral prefrontal cortex (DLPFC) [23]. This increased engagement of the DLPFC increases attention on subsequent trials, resulting in improved performances [24]. Thus, the ACC and DLPFC contribute to the performance of response inhibition trials. A magnetic resonance imaging study showed volume reduction of the

Table 2. Univariate logistic regression analyses of the prevalence of depressive state.

	Crude OR (95% CI)	*P* value
Age	0.98 (0.83–1.15)	0.780
BMI	0.95 (0.69–1.32)	0.779
Appetite	0.95 (0.90–0.99)	0.027
Nocturnal sleeping hours	0.63 (0.28–1.45)	0.281
Difficulty in initiating sleep (yes *vs.* no)	1.33 (0.26–6.74)	0.728
Difficulty in maintaining sleep (yes *vs.* no)	4.36 (0.74–25.74)	0.104
Early morning awakening (yes *vs.* no)	8.00 (1.28–50.04)	0.026
Cultural activities (yes *vs.* no)	0.14 (0.03–0.81)	0.028
Exercise activities (yes *vs.* no)	0.17 (0.03–1.00)	0.050
Finding life worth living (yes *vs.* no)	0.05 (0.01–0.37)	0.003
MMSE score	0.81 (0.54–1.22)	0.308
Cognitive task		
Reaction time		
Task A	92.52 (1.18–7.24×10^3)	0.042
Task B	86.61 (0.94–7.95×10^3)	0.053
Stroop trials	75.15 (1.11–5.09×10^3)	0.045
Non-Stroop trials	1.14×10^2 (1.76–7.43×10^3)	0.026
Stroop minus non-Stroop trials	9.39×10^4 (2.10–4.19×10^9)	0.036
Correction rate		
Task A	0.71 (0.17–2.99)	0.641
Task B	0.81 (0.63–1.04)	0.098
Stroop trials	0.88 (0.76–1.01)	0.064
Non-Stroop trials	1.04 (0.60–1.82)	0.887
Stroop minus non-Stroop trials	0.85 (0.72–1.01)	0.065
Cognistat		
Orientation	–	1.000
Memory	0.98 (0.77–1.26)	0.894
Naming	0.62 (0.33–1.18)	0.144

OR – odds ratio; CI – confidence interval; BMI – body mass index; MMSE – Mini-Mental State Examination.

ACC [25,26] and microstructural abnormalities evaluated using diffusion tensor imaging (DTI) in the white matter of the ACC [27] in patients with geriatric depression, and positron emission tomography studies identified decreased glucose metabolism [28] and cerebral blood flow [29] in the ACC of elderly patients with depression. In addition, depressed elderly patients demonstrated reduced metabolism in the DLPFC [30,31], and patients with geriatric depression showed microstructural abnormalities in the white matter of the DLPFC [32]. These findings suggest that at least some ACC and DLPFC functions are abnormal in the depressive state of the elderly females and these abnormalities contribute to the relationship between the depressive state and impaired performance on response inhibition trials in these females.

The present study has two limitations. First, we performed this study with a limited number of participants and the depressive elderly females. To generalize our results, studies involving a larger number of participants are essential. However, because the factors previously reported to be related to the prevalence of depression, such as awaking in the early morning [33–35], appetite loss [36], lack of interest in cultural and exercise activities [37–39], and finding life not worth living [40], were associated with the prevalence of depressive state, the reliability and validity of our results seem to be ensured. Second, we cannot draw conclusions about cause-and-effect relationships because of the cross-sectional nature of our data.

Conclusions

The present results provide evidence that the impaired response inhibition component of executive function is independently associated with the depressive state of elderly females. Our findings could help clarify the neural mechanisms underlying the depressive state as well as be used in the development of evaluation and treatment methods for the depressive state in elderly females.

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