Dementia and Geriatric Cognitive Disorders Extra

Research Article

Dement Geriatr Cogn Disord Extra 2025;15:19–29
DOI: 10.1159/000542994

Received: April 23, 2024
Accepted: December 2, 2024
Published online: December 9, 2024

Long-Term Multimodal Exercise Intervention for Patients with Frontotemporal Lobar Degeneration: Feasibility and Preliminary Outcomes

Miyuki Nemoto[a] Kiyotaka Nemoto[a] Hiroyuki Sasai[b] Shinji Higashi[c] Miho Ota[a] Tetsuaki Arai[a]

[a]Division of Clinical Medicine, Department of Psychiatry, Institute of Medicine, University of Tsukuba, Tsukuba, Japan; [b]Research Team for Promoting Independence and Mental Health, Tokyo Metropolitan Institute of for Geriatrics and Gerontology, Tokyo, Japan; [c]Department of Psychiatry, Tokyo Medical University, Tokyo, Japan

Keywords

Feasibility · Frontotemporal lobar degeneration · Long-term multimodal exercise intervention · Non-pharmacological intervention

Abstract

Introduction: After Alzheimer's disease, frontotemporal lobar degeneration (FTLD) is the second most common form of early-onset dementia. Despite the heavy burden of care for FTLD, pharmacological and non-pharmacological treatments with sufficient efficacy remain scarce. This study aimed to evaluate the feasibility of a multimodal exercise program for FTLD and to examine preliminary changes in the clinical outcomes of the program in FTLD. ***Methods:*** This single-arm preliminary study was conducted from July 2017 to July 2018 and recruited 4 male patients with FTLD aged 60–78 years. Patients exercised under the supervision of an exercise instructor once every 2 weeks for 48 weeks. The multimodal exercise program comprised cognitive training, moderate-intensity continuous training, strength training, balance training, and flexibility and relaxation training. Feasibility was measured using dropout and attendance rates. Cognitive, psychological, physical, and behavioral function tests were conducted before and after the intervention. ***Results:*** All patients completed the intervention (100%) and attended well (93.6%). Positive changes in scores in the Stroop Color-Word Test (cognitive; 5 out of 6 items), Mood Check List-short form 2 (psychological), movement subscales of the Stereotypy Rating Inventory (behavioral), and Timed Up and Go (TUG, physical) assessments demonstrated a medium-to-high effect size (open effect size: 0.52–0.97). While there were improvements in some domains, such as recovery self-efficacy and exercise efficacy, the MMSE-J scores showed an overall slight decline, especially in the semantic dementia case where a marked decrease was observed. Additionally, three physical function items showed no effect, except for a positive outcome in the TUG test. Functional near-infrared spectroscopy revealed increased activation in the frontal lobe, indicated by elevated oxygenated hemoglobin levels before and after the exercise intervention. This pattern of activation suggests that the intervention may have stimulated neural activity in the frontal lobe, potentially enhancing cognitive and behavioral functions, including executive function and attention. ***Conclusion:*** The long-term multimodal exercise intervention may be feasible and positively change the cognitive, psychological, physical, and behavioral functions

karger@karger.com
www.karger.com/dee

Karger
OPEN ACCESS

Correspondence to:
Miyuki Nemoto, miyuki.nemoto@md.tsukuba.ac.jp

in older adults with FTLD. Although the intervention led to improvements in certain areas, there were also declines observed in various functions, which may not necessarily be due to the intervention itself but rather reflect the natural progression of the disease.

Introduction

Frontotemporal lobar degeneration (FTLD) is the second most common form of early-onset dementia in individuals aged <65 years, following Alzheimer's disease [1]. It is classified into three types: behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SD), and progressive nonfluent aphasia [2, 3]. FTLD is a challenging form of dementia because of its unique clinical symptoms, such as disinhibition, apathy, and ritualistic behavior [4]. FTLD primarily affects patients with early-onset dementia, creating significant challenges for caregivers and imposing substantial economic and emotional burdens on both families and healthcare systems [5]. Nevertheless, no effective pharmacological or non-pharmacological treatments for FTLD have been established to date.

Non-pharmacological interventions for dementia appear promising, and exercise-based interventions are particularly effective [6–9]. Exercise-induced expression of brain-derived neurotrophic factors is considered to promote neural regeneration, improve glucose tolerance and insulin resistance, and activate the frontal lobes, which are the mechanisms underlying dementia prevention [10].

Memory, motor function (excluding FTLD-motor neuron disease), and visuospatial cognitive function are preserved in patients with FTLD [11]; therefore, tasks based on motor function can be easily introduced [12]. Additionally, symptoms of heightened susceptibility to environmental influences may make exercise a habit and incorporate it into regular activities, a strategy known as routine-based therapy [13]. Despite reports of exercise-based interventions for Alzheimer's disease [14], only a few case reports on such interventions for FTLD are available [15, 16]. Multimodal intervention is reportedly effective for dementia [17]. However, previous studies primarily involved short- to medium-term (12–24 weeks) interventions and unimodal training. Notably, the efficacy of long-term and multimodal interventions, specifically in FTLD, is largely unknown. Moreover, researchers have not indicated the outcomes, except for physical function, in multiple patients with FTLD. While certain types of exercise may help alleviate specific symptoms of FTLD, these benefits are often restricted to a limited range of symptoms. To address the full spectrum of FTLD manifestations, a multimodal approach is necessary. Unlike single exercise types, a multimodal regimen can engage and stimulate multiple brain regions, potentially offering broader and more comprehensive therapeutic benefits.

The present study aimed to investigate in clinical outcomes following a long-term multimodal exercise intervention for FTLD. Specifically, we sought to evaluate the feasibility of the program and assess preliminary effects on cognitive, psychological, physical, and behavioral functions. We hypothesized that the exercise intervention would be feasible and would lead to improvements across these domains. Regarding functional near-infrared spectroscopy (fNIRS), we anticipated that the intervention would increase activation in the prefrontal cortex, given its central role in cognitive control and physical coordination. As this was a preliminary study, the intervention was initially applied to a small sample.

Methods

Study Design

This 48-week single-arm study was conducted at the University of Tsukuba Hospital in Tsukuba City, Ibaraki, Japan, from July 2017 to July 2018. The intervention involved physical exercise for patients with FTLD. A single-arm design without a control group was adopted because the study was preliminary. The study protocol followed the tenets of the Declaration of Helsinki was approved by the Ethics Committee of University of Tsukuba Hospital (approval number: H30-228) and was registered in the UMIN Clinical Trials Registry (No. UMIN000035097).

Participants

Patients with FTLD were recruited according to the FTLD criteria for bvFTD and SD [18, 19]. We did not limit recruitment to specific subtypes of FTLD; however, most participants who met the inclusion criteria were diagnosed with the bvFTD or SD, which is why these two subtypes were primarily represented in the study. The inclusion criteria were as follows: (i) age >60 years, (ii) ambulatory status with or without assistance, and (iii) ability to tolerate functional testing and exercise. The exclusion criteria were as follows: (i) terminal disease and (ii) major musculoskeletal conditions (e.g., severe joint

Table 1. Characteristics of the participants

	Patient A	Patient B	Patient C	Patient D
Demographics and anthropometrics				
Sex	Male	Male	Male	Male
Age, years	60	77	61	78
Height, cm	181.0	159.8	173.9	159.8
Weight, kg	90.1	56.0	71.2	52.0
Body mass index, kg/m^2	27.5	21.9	23.5	20.4
Barthel index, points	85	85	95	100
Education, years	16	12	12	12
Diagnosis	bvFTD	bvFTD	bvFTD	SD
Duration, years	1.0	2.5	4.3	4.0
Medical history				
Diagnosed comorbidities, *n*[a]	3	3	1	4
Prescribed medications, *n*[b]	5	6	2	10

Data are shown as mean (standard deviation) for continuous variables. bvFTD, behavioral variant frontotemporal dementia; SD, semantic dementia. [a]Previously diagnosed conditions and conditions identified within physician screen at baseline assessment. [b]Number of medications including prescribed supplements.

disorders, fractures, or chronic pain syndromes), cardiovascular conditions (e.g., congestive heart failure, severe hypertension, or recent heart attacks), or other neurological conditions (e.g., stroke, epilepsy, or advanced Parkinson's disease) precluding exercise. Table 1 presents the patients' characteristics. Four male patients with FTLD met the eligibility criteria and were enrolled in the study. Among these, 3 patients had bvFTD, whereas 1 had SD.

Intervention

The intervention program was provided under the following conditions: (i) participation with a partner (required but without specific guidance to partner), (ii) individualized exercise instructions, and (iii) a combination of regular hospital and home exercises. The patients engaged in a multimodal exercise program, which comprised cognitive training, moderate-intensity continuous training (MICT) [20], strength training, balance training, and flexibility and relaxation training. An exercise instructor provided the one-on-one program in a medically supervised university hospital for 60 min per day, once every 2 weeks, for 48 weeks.

The program included a 5-min warm-up, 10 min of dual task training, 10–30 min of MICT (on rowing ergometer; Technogym, Japan) at 40%–70% heart rate $(HR)_{peak}$, 10–30 min of strength training, 10 min of balance training, and 5-min flexibility and relaxation. Table 2 shows the details of the multimodal exercise program. All exercises were performed at a moderate intensity (rate of perceived exertion [21] of 11–13 and 40%–70% HR_{peak} by Polar A360 [Polar Electro., Kemple, Finland]). The patients were provided with home-based exercises (one type of exercise program per month: strength training, aerobic exercise, flexibility, and relaxation) tailored to their fitness level and instructed to perform them regularly.

Feasibility Assessment

The feasibility of the exercise program in the hospital used the dropout rate (proportion of patients who did not complete the post-intervention assessment), attendance rate (number of attendances/total number of sessions), diary review, and exercise persistence status (i.e., incorporation of exercise into daily life). The patients were instructed to record their daily exercises and impressions of the program in a printed diary. An exercise instructor reviewed each diary to assess the exercise routine at home and the patients' impressions of the program. We evaluated the exercise persistence status with home exercise adherence rate from the diary (percentage of exercise days, divided by scheduled exercise date), action plans [22], recovery self-efficacy (Re-SE) [23], and exercise self-efficacy [24].

Outcome Assessments

All outcome measures were assessed before and after the 48-week intervention by trained staff members, including a clinical psychologist. The following items were investigated: anthropometric variables, self-reported measures of physical function [25, 26], cognitive function [27–29], psychological

Table 2. Multimodal exercise program

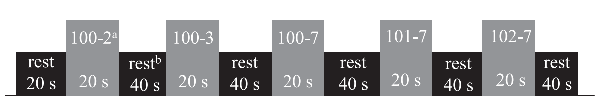
Menu	Contents
Warm-up (5 min)	• 2 min of mobility and range of motion exercises for every joint in the body • 2 min of low- to moderate-intensity aerobic movements using legs and arms • 1 min of dynamic flexibility
Dual task training (10 min)	• 12 cognitive programs based on dual task (1 type of program/month) • Examples: While bending the fingers of one hand in order, bend the fingers of the other hand in reverse order, calculate while stepping in place, clap on multiples of three while stepping in place
MICT program (10–30 min)	• Week 1–4 : 50% of HR_{peak}, 10 min (intensity, time) • Week 5–12: 50% of HR_{peak}, 20 min (intensity, time) • Week 13–20: 50% of HR_{peak}, 30 min (intensity, time) • Week 21–28: 60% of HR_{peak}, 30 min (intensity, time) • Week 29–36: 65% of HR_{peak}, 30 min (intensity, time) • Week 37–48: 70% of HR_{peak}, 30 min (intensity, time)
Strength training (10–20 min)	• 12 strength programs (1 type of program/month) • Examples: upper limbs: arm curls, shoulder press (using a machine), trunk: plank, hip lift, lower limbs: squats, leg curls (using a machine)
Balance training (10 min)	• 12 balance programs (1 type of program/month) • Examples: single-leg knee raise, tandem stance, tandem walk, heel-to-toe walk, exercise ball program (sitting, sit up on the ball, etc.)
Flexibility and relaxation (5 min)	• Flexibility training: stretching exercises, yoga, or Pilates focused on increasing flexibility, reducing muscle stiffness, and enhancing overall mobility • Relaxation training: deep breathing exercises, progressive muscle relaxation, or meditation, designed to help participants relax both their body and mind

MICT, moderate-intensity continuous training.

functions [30, 31], physical function tests [32–35], behavioral function [23, 24, 36], and fNIRS. Details of outcome measures are described in the online supplementary materials (for all online suppl. material, see https://doi.org/10.1159/000542994). A description of fNIRS is provided in the next section.

Functional Near-Infrared Spectroscopy

fNIRS was used to assess frontal lobe function. fNIRS measurements were performed during a modified serial number task (Fig. 1). The patients performed subtraction drills (five questions, 20 s each) that appeared on the monitor. A 40 s rest interval was allowed between each task, during which patients were instructed to pronounce nonsense vowels (a, i, u, e, and o). fNIRS data were collected using a continuous three-wavelength fNIRS LABNIRS 67ch system with an entire head holder (Shimadzu, Japan). Subsequently, we arranged 54 channels to measure the dorsolateral prefrontal, parietal, somatosensory, and forehead regions [37]. We digitized each patient's channel position using the Fastrak 3D digitizer (Polhemus, USA) and inputted the data into the standard brain model. Next, we obtained the Montreal Neurological Institute coordinate outputs using the NIRS-SPM software Ver. 4 (Department of Bio and Brain Engineering, KAIST, Korea) to extract brain anatomical information from measurement channels. The NIRS system measured oxyhemoglobin (HbO) and decreased deoxyhemoglobin levels following changes in their cortical concentration based on the modified Beer-Lambert law.



[a]Subtraction: five questions, 20s each; 100 minus 2, 100 minus 3, etc.
[b]Rest: 40s each; pronounce nonsense vowels (a, i, u, e, and o).

Fig. 1. Modified serial number task.

Statistical Analysis

Values are expressed as means and standard deviations at baseline. The 48-week changes in all outcome measures are expressed as means, standard deviations, and effect sizes

Table 3. Cognitive and psychological functions following 48-week exercise program (N = 4)

Outcomes	Pre		Post		Cohen's *d*	The range of pre-post differences			
						patient A	patient B	patient C	patient D
Cognitive functions									
MMSE, points	20.8	(5.9)	19.5	(11.3)	0.15	3.0	2.0	−1.0	−9.0
FAB, points	11.3	(3.6)	10.5	(5.6)	0.17	3.0	1.0	−4.0	−3.0
SCWT									
Control condition									
Reaction time, ms	666.9	(42.1)	663.3	(96.6)	0.05	0.2	−92.6	−32.8	110.5
Number of errors, *n*	38.0	(10.6)	37.0	(12.2)	0.09	3.0	9.0	−26.0	10.0
Match condition									
Reaction time, ms	663.3	(52.4)	670.6	(73.1)	0.12	−0.8	−19.2	−2.2	51.4
Number of errors, *n*	39.5	(9.4)	37.2	(9.6)	0.24	0.0	−1.0	−19.0	11.0
Mismatch condition									
Reaction time, ms	672.8	(47.6)	621.1	(7.9)	0.52	4.4	−85.7	−37.1	−88.4
Number of errors, *n*	43.5	(3.7)	43.0	(10.6)	0.06	−10.0	11.0	−13.0	10.0
Psychological functions									
MCL-S.2									
Pleasantness	17.2	(7.2)	21.9	(6.6)	0.68	2.6	4.5	−1.0	8.4
Relaxation	17.3	(6.9)	21.9	(6.0)	0.71	3.3	2.5	−0.7	8.0
Anxiety	11.7	(6.5)	10.3	(6.7)	0.21	−0.3	1.0	−0.5	−2.6
GDS, points	3.3	(2.6)	1.8	(1.7)	0.68	−3.0	3.0	−1.0	−5.0

Data are presented as mean (standard deviation) and frequency (percentage) for categorical variables. MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; SCWT, Stroop Color-Word Test; MCL-S.2, the Mood Check List-short form 2; GDS-S-J, the Geriatric Depression Scale-Short Version-Japanese.

(Cohen's *d*) to better interpret the intensity of within-group changes. Data were analyzed using IBM SPSS Statistics for Windows version 22 (IBM Corp., Armonk, NY, USA). fNIRS data analysis was conducted using the NIRS-SPM software operated in the MATLAB environment (MathWorks, Natick, MA, USA) [38]. In the analyzing process, after removing artifacts due to body movement, a predictive model of HbO and deoxyhemoglobin response was generated based on the general linear model to examine the transition of brain activity sites before and after exercise intervention. SPM t-statistic maps were created with significance for HbO set at $p < 0.01$.

Results

After 48 weeks, all patients completed the post-intervention assessments, with a mean attendance rate of 93.6% (range, 88.2–100%). Based on a diary review, positive opinions included "exercise refreshes the mood," "exercise has become a habit," and "exercise is fun." Negative opinions included "exercise makes me a little tired." The program ended without injuries or other adverse events. The home exercise adherence rate based on the information in the diaries was 68.5% (range, 60.8–77.7%), and the diary collection rate (percentage of activity diaries successfully collected from participants) was 83.1% (range, 54.5–100.0%). Participants were instructed to submit their activity diaries on a monthly basis.

Table 1 presents the characteristics of the participants. The Barthel index scores were as follows: participants A and B both scored 85 points, participant C scored 95 points, and participant D achieved a perfect score of 100 points.

Table 3 presents the cognitive and psychological function values before and after the intervention. The changes in MMSE-J scores before and after the intervention showed improvement in two out of three cases of bvFTD, with scores increasing from 25 to 28 and from 23 to 25, respectively. However, in the third case of bvFTD, the score slightly decreased from 23 to 22. In contrast, the SD case exhibited a strongly decline, with the score dropping from 12 to 3. Overall, the MMSE-J scores reflected a small deterioration, indicating a small effect. Similarly, the FAB scores showed a slight overall decline. In the SCWT results, five items showed improvement, while one item showed deterioration.

Table 4. Behavioral and physical functions following 48-week exercise program (N = 4)

Outcomes	Pre		Post		Cohen's d	The range of pre-post differences			
						patient A	patient B	patient C	patient D
Behavioral functions									
Integration into lifestyle pattern, yes, n	2	(50.0%)	4	(100.0%)		1.0	0.0	0.0	1.0
Time of exercise, regularly scheduled, yes, n	2	(50.0%)	4	(100.0%)		1.0	0.0	0.0	1.0
Recovery self-efficacy	2.3	(1.5)	3.5	(1.3)	0.86	2.0	1.0	0.0	2.0
Exercise self-efficacy	9.0	(2.7)	15.0	(8.3)	0.97	2.0	15.0	7.0	0.0
SRI total	10.5	(9.0)	10.3	(6.1)	0.03	7.0	11.0	−16.0	−3.0
Eating and cooking	0.8	(1.5)	2.0	(4.0)	0.40	5.0	0.0	0.0	0.0
Roaming	2.5	(3.0)	2.0	(4.0)	0.56	0.0	4.0	−6.0	0.0
Speaking	2.0	(2.8)	3.8	(1.7)	0.78	2.0	4.0	−2.0	3.0
Movements	1.5	(3.0)	0.0	(0.0)	0.71	0.0	0.0	−6.0	0.0
Daily rhythm	3.8	(2.9)	2.5	(1.7)	0.55	0.0	3.0	−2.0	−6.0
Physical functions									
Grip strength, kg	30.42	(8.20)	29.76	(8.08)	0.08	3.9	−0.5	−4.7	−1.3
One-leg stance, s	36.18	(27.35)	38.37	(25.48)	0.08	1.3	−9.3	0.0	16.8
Timed Up and Go, s	7.36	(1.16)	6.54	(1.27)	0.68	−0.9	4.2	−1.1	−1.7
Usual gait speed, s	3.96	(1.23)	3.98	(0.75)	0.02	−0.3	−0.9	0.2	1.1

Data are shown as mean (standard deviation) for continuous variables and frequency (percentage) for categorical variables. SRI, the Stereotypy Rating Inventory.

Despite these changes, most of the effect sizes were small, except for one improvement with a medium effect size of d = 0.52 in the mismatch condition (reaction time). The MCL-S.2 results showed three improvements, with two items – pleasantness and relaxation – exhibiting medium effect sizes of d = 0.68 and d = 0.71, respectively. Another item showed a small effect on anxiety. The GDS results indicated an improvement with a medium effect size of d = 0.68.

Table 4 presents the behavioral and physical function values before and after the intervention. All patients reported that the exercise regimen became an integrated part of their daily lives following the intervention. Both Re-SE and exercise efficacy showed significant improvements, with large effect sizes (d > 0.8). In the SRI results, overall stereotypical behaviors slightly decreased. However, specific increases were noted in areas such as eating, cooking, and speaking, while reductions were observed in roaming, movement, and daily rhythm (Cohen's d = 0.56–0.71). For physical function, three items showed no effect, but one item demonstrated a positive effect on the TUG test (Cohen's d = 0.68). Figure 2 shows the fNIRS results of patients. After the intervention, activation of the frontal lobe was observed in all patients.

Discussion

The current study evaluated the feasibility of the exercise program and observed changes in the clinical outcomes of a long-term multimodal exercise intervention for FTLD. We hypothesized that the exercise program is feasible and may positively change the cognitive, psychological, physical, and behavioral functions of individuals with FTLD. Our preliminary findings largely supported the hypothesis, showing improvements in specific areas. However, declines were also observed in several functions, which may not necessarily be attributable to the intervention and could instead reflect the natural progression of FTLD.

Program Feasibility

The exercise program in the study might be feasible for the following reasons. The attendance and dropout rates were notably high at 93.6% and 0%, respectively, whereas the home exercise adherence rate was seemed moderately high (68.5%). Considering the characteristic regional atrophy of the frontal and temporal lobes in FTLD [39], patients usually experience difficulty while continuously participating in exercise programs. For example, atrophy

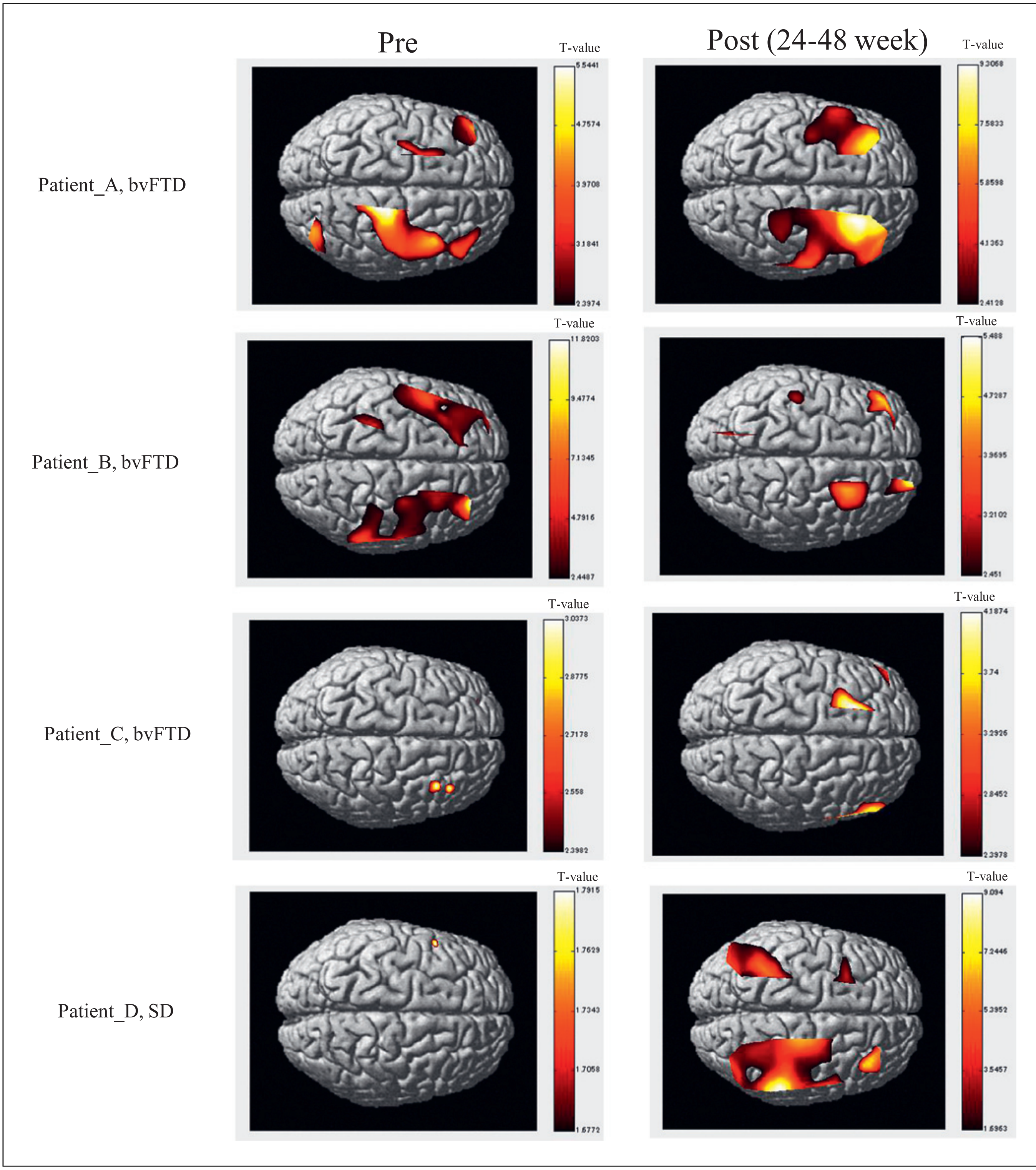


Fig. 2. Results of near-infrared spectroscopy (NIRS)-SPM analysis.

of the anterior cingulate cortex is associated with apathy in FTLD, and dysfunction of the right temporal lobe is linked to disinhibition [40]. However, we obtained high attendance, low dropout rates, and home exercise adherence rates, which were established in daily life. All patients reported that they could integrate exercise into their daily lives and that their exercise time was regularly scheduled after the intervention. Furthermore, Re-SE and exercise self-efficacy showed positive changes. Patients' feedback on the multimodal exercise intervention was generally positive. The exercise program in the study could be selected according to an individual's level of fitness, and exercise at home was established according to individual characteristics. Additionally, the exercise instructor supported the exercise continuation at home, providing feedback on the diary (encouragement and praise). Therefore, this exercise program might have been more acceptable to the patients.

The presence of partners who provided support for the exercise intervention might have been important. For people with dementia, interventions with a partner have the potential to enhance well-being and satisfaction for both the partner and patient [41, 42]. For those with FTLD, activity-based interventions with a partner have also been suggested to alleviate behavioral symptoms [43]. Particularly in FTLD, it is crucial to provide fixed caregiver support owing to the symptoms of heightened susceptibility to environmental influences [44]. Participation in the exercise program with a partner would be considered to play an important role in this study.

FTLD is often challenging to manage due to its characteristic symptoms, such as stereotypic behavior and disinhibition. In this study, however, we implemented a 48-week exercise program for FTLD, which appeared feasible under the following conditions: (i) participation with a partner, (ii) individualized exercise instructions, and (iii) a combination of regular hospital and home exercises. Such feasibility may be attributed to the management of the symptom of heightened susceptibility to environmental influences.

Changes in Frontal Lobe Function

In fNIRS, frontal lobe activation was visually observed before and after the exercise intervention. Previous fNIRS and MRI studies reported that an exercise intervention activated the frontal lobes in cognitively normal individuals and patients with MCI/AD [45, 46]. However, there are no reports on FTLD. This is the first report on FTLD to demonstrate that exercise may effectively activate the frontal lobes, even in FTLD cases in which the frontal lobes have degenerated and become atrophied. Furthermore, positive changes were observed in items related to the frontal lobe, such as cognitive function emotion. These findings suggest that the frontal lobe activation induced by the exercise intervention may be involved in the effects on cognitive, behavioral, psychological, and physical functions, as discussed in detail below.

Changes in Cognitive Functions

The SCWT is a cognitive function test that assesses frontal lobe function [47]. While the SCWT results suggest that exercise may have a beneficial effect on frontal lobe function, the observed changes were not uniformly positive. Specifically, out of six cases, five showed improvements, but one case exhibited deterioration. The overall effects were small, with only one improvement reaching a medium effect size. The observed positive changes in SCWT scores before and after exercise intervention are noteworthy results in FTLD. Atrophy can be observed in the frontal and temporal lobes, with specific symptoms in FTLD [48]. There were also positive changes in global cognitive function. In patients with bvFTD, the MMSE-J scores after the intervention were either improved or remained slightly decreased. In contrast, in the patient with SD, a marked decrease was noted, possibly because of differences in the pathophysiology of both diseases. Specifically, in SD where semantic dysfunction is the primary symptom [49, 50], even mild disease progression may result in a greater loss of points on the MMSE-J, a test strongly influenced by the degree of language comprehension. While previous studies have reported the effects of exercise interventions on physical function, changes in cognitive function through exercise intervention have not been previously documented on FTLD [46].

Changes in Psychological Functions

Our findings suggest that multimodal exercise interventions positively influence psychological functions, particularly emotional functions. Previous studies have reported that physical activity and exercise may improve the psychological symptoms of dementia [51]. In this study, the positive changes in pleasant and relaxed emotions after the intervention may be attributed to exercise, even in patients with FTLD. Despite reports of changes in emotional expression (blunting of emotions) in FTLD, particularly in bvFTD and SD [52], changes in emotions before and after exercise intervention in FTLD remain unknown.

Changes in Behavioral Functions

After the multimodal exercise intervention, changes in stereotypical behavior were observed in patients with FTLD. In SRI, we observed a positive change in roaming, movement, and daily rhythm, with a moderate effect size, particularly for movement. It should also be noted that two dimensions of stereotypical behavior – speaking and eating and cooking – worsened, and the overall sum score of SRI did not change significantly. Nevertheless, the beneficial changes in motion-related items (roaming, movement, and daily rhythm) are noteworthy and considered an outcome of the intervention. To our knowledge, changes in SRI through exercise intervention have not been previously reported in FTLD.

Changes in Physical Functions

Based on our study findings, multimodal exercise intervention may positively affect physical function in patients with FTLD. Previous studies have shown that exercise intervention improves physical function in patients with bvFTD [15, 16]. In our study, a positive change was observed in the Timed Up and Go (TUG) test; however, the other three physical function measurements did not show any significant effects. While these preliminary findings are promising for TUG, they should be interpreted cautiously in the context of the overall physical function results. The effect of exercise intervention might have been easier to achieve as FTLD usually has an early-onset, and the patients report relatively well-preserved physical fitness.

Strengths and Limitations

The strength of this study lies in being the first long-term multimodal exercise intervention for FTLD globally. This is the first study to conduct a 48-week exercise intervention in multiple cases of FTLD, which is considered difficult to manage, and to evaluate the effect of exercise intervention from multiple perspectives. However, it is important to interpret the results cautiously because of the limited sample size and single-arm nature of the study. Despite these limitations, this study contributes to the emerging understanding of the potential benefits of exercise interventions for FTLD, warranting further research. This study was designed to observe changes specific to FTLD before and after the intervention by scientifically measuring various aspects of patients, including cognition, physical, psychological, and behavioral aspects. However, this study had some limitations. First, the single-arm design, limited sample size, and lack of a control group limit the ability to determine the effectiveness of the intervention. Specifically, the lack of a control group prevents comparison to confirm the effects of the intervention. Determining the certainty of the effects and causal relationships can be difficult. Furthermore, assessing how changes over time and other factors, such as learning effects, aging, and regression to the mean, may influence the outcomes is challenging. Second, we did not consider examination or evaluator blinding. A lack of blinding may lead to a biased evaluation and assessment. Therefore, these issues should be addressed in future studies. We intend to perform a small pilot randomized controlled trial to obtain a less biased effect size estimate. Specifically, the examination will introduce randomization and blinding of the assessors. Furthermore, we also aim to design a large-scale randomized controlled trial to test the effectiveness of this program on cognitive function.

Conclusion

This novel study reports the feasibility and changes in clinical outcomes of long-term multimodal exercise for FTLD. This multimodal exercise intervention is a feasible program for patients with FTLD. Additionally, this intervention might positively change clinical outcomes, such as frontal lobe, cognitive, psychological, behavioral, and physical functions in patients with FTLD. However, further studies should use a randomized design to assess the efficacy of multimodal exercise intervention on a larger scale.

Acknowledgments

We are grateful to the patients and staff involved in this study.

Statement of Ethics

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of University of Tsukuba Hospital (approval No. H30-228). All participants provided written informed consent after receiving a thorough explanation of the study's purpose, procedures, and potential risks. For all participants with cognitive impairments, consent was obtained in the presence of a family member, and the participant's signature was still required, in accordance with ethical guidelines.

Conflict of Interest Statement

Shimadzu Corporation provided the fNIRS equipment used in this study and assisted with the technical aspects of data analysis related to the fNIRS measurements. This provision of equipment and assistance may be perceived as a potential conflict of interest due to the possibility of influencing the study's outcomes. However, we want to emphasize that the study design, data collection, interpretation of results, and conclusions were conducted independently by the research team, ensuring the integrity and objectivity of the research.

Funding Sources

This research was funded by JSPS KAKENHI (Grant No. JP17K13218) and supported by Shimadzu Corporation, which provided the fNIRS equipment for this study. The funder had no role in the design, data collection, data analysis, and reporting of this study.

Author Contributions

M.N. made substantial contributions to the conceptualization and design of the study. M.N., S.H., and H.S. were responsible for the methodology and formal analysis, with all authors actively participating in the investigation. T.A. and K.N. provided essential resources, while M.N. and M.O. managed data curation. The original draft of the manuscript was prepared by M.N. and H.S., and all authors contributed to the critical review and revision of the manuscript for significant intellectual content. T.A. supervised the project, with project administration handled by M.N. and A.T. Funding acquisition was managed by M.N. and T.A. All authors have approved the final version of the manuscript and are committed to ensuring accountability for all aspects of the work, addressing any concerns regarding the accuracy or integrity of the study as needed.

Data Availability Statement

The data presented in this study are available upon request from the corresponding author. The data are not publicly available owing to privacy concerns.

References

1 Grossman M, Seeley WW, Boxer AL, Hillis AE, Knopman DS, Ljubenov PA, et al. Frontotemporal lobar degeneration. Nat Rev Dis Primers. 2023;9(1):40. https://doi.org/10.1038/s41572-023-00447-0
2 Antonioni A, Raho EM, Lopriore P, Pace AP, Latino RR, Assogna M, et al. Frontotemporal dementia, where do we stand? A narrative review. Int J Mol Sci. 2023;24(14):11732. https://doi.org/10.3390/ijms241411732
3 Snowden JS. Changing perspectives on frontotemporal dementia: a review. J Neuropsychol. 2023;17(2):211–34. https://doi.org/10.1111/jnp.12297
4 Young JJ, Lavakumar M, Tampi D, Balachandran S, Tampi RR. Frontotemporal dementia: latest evidence and clinical implications. Ther Adv Psychopharmacol. 2018;8(1):33–48. https://doi.org/10.1177/2045125317739818
5 Galvin JE, Howard DH, Denny SS, Dickinson S, Tatton N. The social and economic burden of frontotemporal degeneration. Neurology. 2017;89(20):2049–56. https://doi.org/10.1212/WNL.0000000000004614
6 Kouloutbani K, Karteroliotis K, Politis A. The effect of physical activity on dementia. Psychiatriki. 2019;30(2):142–55. https://doi.org/10.22365/jpsych.2019.302.142
7 Cass SP. Alzheimer's disease and exercise: a literature review. Curr Sports Med Rep. 2017;16(1):19–22. https://doi.org/10.1249/JSR.0000000000000332
8 Du Z, Li Y, Li J, Zhou C, Li F, Yang X. Physical activity can improve cognition in patients with Alzheimer's disease: a systematic review and meta-analysis of randomized controlled trials. Clin Interv Aging. 2018;13:1593–603. https://doi.org/10.2147/CIA.S169565
9 Song D, Yu DSF. Effects of a moderate-intensity aerobic exercise programme on the cognitive function and quality of life of community-dwelling elderly people with mild cognitive impairment: a randomised controlled trial. Int J Nurs Stud. 2019;93:97–105. https://doi.org/10.1016/j.ijnurstu.2019.02.019
10 Huang H, Li W, Qin Z, Shen H, Li X, Wang W. Physical exercise increases peripheral brain-derived neurotrophic factors in patients with cognitive impairment: a meta-analysis. Restor Neurol Neurosci. 2021;39(3):159–71. https://doi.org/10.3233/RNN-201060
11 Piguet O, Hornberger M, Mioshi E, Hodges JR. Behavioural-variant frontotemporal dementia: diagnosis, clinical staging, and management. Lancet Neurol. 2011;10(2):162–72. https://doi.org/10.1016/S1474-4422(10)70299-4
12 Shinagawa S, Nakajima S, Plitman E, Graff-Guerrero A, Mimura M, Nakayama K, et al. Non-pharmacological management for patients with frontotemporal dementia: a systematic review. J Alzheimers Dis. 2015;45(1):283–93. https://doi.org/10.3233/JAD-142109
13 Vlotinou P, Tsiakiri A, Detsaridou G, Nikova A, Tsiptsios D, Vadikolias K, et al. Occupational therapy interventions in patients with frontotemporal dementia: a systematic review. Med Sci. 2023;11(4):71. https://doi.org/10.3390/medsci11040071
14 López-Ortiz S, Lista S, Valenzuela PL, Pinto-Fraga J, Carmona R, Caraci F, et al. Effects of physical activity and exercise interventions on Alzheimer's disease: an umbrella review of existing meta-analyses. J Neurol. 2023;270(2):711–25. https://doi.org/10.1007/s00415-022-11454-8
15 Schmidt J, Combs K, Neely L. Moderate-intensity exercise in an individual with frontotemporal dementia: a case report. Case Rep Rev Open Access. 2021;2:123.
16 Fukuda T, Fukumura K, Uchida Y, Ootsuka T, Yasuda T, Iida H, et al. A case of dementia presenting remarkable improvement in activities of daily living through KAATSU training. Int J KAATSU Train Res. 2011;7(1):13–7. https://doi.org/10.3806/ijktr.7.13
17 Venegas-Sanabria LC, Cavero-Redondo I, Martínez-Vizcaino V, Cano-Gutierrez CA, Álvarez-Bueno C. Effect of multicomponent exercise in cognitive impairment: a systematic review and meta-analysis. BMC Geriatr. 2022;22(1):617. https://doi.org/10.1186/s12877-022-03302-1
18 Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011;134(Pt 9):2456–77. https://doi.org/10.1093/brain/awr179
19 Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. Neurology. 2011;76(11):1006–14. https://doi.org/10.1212/WNL.0b013e31821103e6
20 ACOS Medicine. ACSM's guidelines for exercise testing and prescription. 10th ed. Alphen aan den Rijn: Wolters Kluwer; 2017.
21 Borg G. Perceived exertion as an indicator of somatic stress. J Rehabil Med. 1970;2(2):92–8. https://doi.org/10.2340/1650197719702239298
22 Nakano S, Okuno J, Fukazaku T, Hotta T, Yabushita N, Nemoto M, et al. Factors associated with maintenance of physical activity among older adults who participated in the class in a care prevention program. Phys Ther Jpn. 2015;42:511–8.

23 Schwarzer R, Luszczynska A, Ziegelmann JP, Scholz U, Lippke S. Social-cognitive predictors of physical exercise adherence: three longitudinal studies in rehabilitation. Health Psychol. 2008;27(1S):S54–63. https://doi.org/10.1037/0278-6133.27.1(Suppl.).S54
24 Oka K. Stages of change for exercise behavior and self-efficacy for exercise among middle-aged adults. Nihon Koshu Eisei Zasshi. 2003;50(3):208–15.
25 Mahoney FI, Barthel DW. Functional evaluation: the barthel Index. Md State Med J. 1965;14:61–5.
26 Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9(3 Part 1):179–86. https://doi.org/10.1093/geront/9.3_part_1.179
27 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):189–98. https://doi.org/10.1016/0022-3956(75)90026-6
28 Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol. 1935;18(6):643–62. https://doi.org/10.1037/h0054651
29 Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a frontal assessment battery at bedside. Neurology. 2000;55(11):1621–6. https://doi.org/10.1212/wnl.55.11.1621
30 Kimio H, Masahiko M. Reliability and validity of the reversed Mood Check List-short form 2 (MCL-S.2) measuring the positive mood state following exercise. J Health Sci Kyushu Univ. 2011;33:21–6.
31 Brink TL, Yesavage JA, Lum O, Heersema PH, Adey M, Rose TL. Screening tests for geriatric depression. Clin Gerontol. 1982;1(1):37–43. https://doi.org/10.1300/j018v01n01_06
32 Shinkai S, Kumagai S, Fujiwara Y, Amano H, Yoshida Y, Watanabe S, et al. Predictors for the onset of functional decline among initially non-disabled older people living in a community during a 6-year follow-up. Geriatr Gerontol Int. 2003;3(s1):S31–9. https://doi.org/10.1111/j.1444-0594.2003.00094.x
33 Rikli R, Busch S. Motor performance of women as a function of age and physical activity level. J Gerontol. 1986;41(5):645–9. https://doi.org/10.1093/geronj/41.5.645
34 Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991;39(2):142–8. https://doi.org/10.1111/j.1532-5415.1991.tb01616.x
35 Shinkai S, Watanabe S, Kumagai S, Fujiwara Y, Amano H, Yoshida H, et al. Walking speed as a good predictor for the onset of functional dependence in a Japanese rural community population. Age Ageing. 2000;29(5):441–6. https://doi.org/10.1093/ageing/29.5.441
36 Shigenobu K, Ikeda M, Fukuhara R, Maki N, Hokoishi K, Nebu A, et al. The Stereotypy Rating Inventory for frontotemporal lobar degeneration. Psychiatry Res. 2002;110(2):175–87. https://doi.org/10.1016/s0165-1781(02)00094-x
37 Nakamura S, Yomota S, Ito H, Akinaga N, Hori A, Chinomi K, et al. A novel cognitive function scale using functional near-infrared spectroscopy for evaluating cognitive dysfunction. J Alzheimers Dis. 2021;81(4):1579–88. https://doi.org/10.3233/JAD-210072
38 Ye JC, Tak S, Jang KE, Jung J, Jang J. NIRS-SPM: statistical parametric mapping for near-infrared spectroscopy. Neuroimage. 2009;44(2):428–47. https://doi.org/10.1016/j.neuroimage.2008.08.036
39 Lu PH, Mendez MF, Lee GJ, Leow AD, Lee HW, Shapira J, et al. Patterns of brain atrophy in clinical variants of frontotemporal lobar degeneration. Dement Geriatr Cogn Disord. 2013;35(1–2):34–50. https://doi.org/10.1159/000345523
40 Borroni B, Grassi M, Premi E, Gazzina S, Alberici A, Cosseddu M, et al. Neuroanatomical correlates of behavioural phenotypes in behavioural variant of frontotemporal dementia. Behav Brain Res. 2012;235(2):124–9. https://doi.org/10.1016/j.bbr.2012.08.003
41 Ingersoll-Dayton B, Spencer B, Kwak M, Scherrer K, Allen RS, Campbell R. The couples life story approach: a dyadic intervention for dementia. J Gerontol Soc Work. 2013;56(3):237–54. https://doi.org/10.1080/01634372.2012.758214
42 Orsulic-Jeras S, Whitlatch CJ, Powers SM, Johnson J. A dyadic perspective on assessment in Alzheimer's dementia: supporting both care partners across the disease continuum. Alzheimers Dement. 2020;6(1):e12037. https://doi.org/10.1002/trc2.12037
43 O'Connor CM, Clemson L, Brodaty H, Low LF, Jeon YH, Gitlin LN, et al. The tailored activity program (TAP) to address behavioral disturbances in frontotemporal dementia: a feasibility and pilot study. Disabil Rehabil. 2019;41(3):299–310. https://doi.org/10.1080/09638288.2017.1387614
44 Ikeda M. Symptomatology of frontotemporal lobar degeneration. Proceeding Annu Meet Jpn Res Group Senile Demen. 2012;19:92–7. (in Japanese).
45 Liao YY, Chen IH, Hsu WC, Tseng HY, Wang RY. Effect of exergaming versus combined exercise on cognitive function and brain activation in frail older adults: a randomised controlled trial. Ann Phys Rehabil Med. 2021;64(5):101492. https://doi.org/10.1016/j.rehab.2021.101492
46 Haeger A, Costa AS, Schulz JB, Reetz K. Cerebral changes improved by physical activity during cognitive decline: a systematic review on MRI studies. Neuroimage Clin. 2019;23:101933. https://doi.org/10.1016/j.nicl.2019.101933
47 Scsrpina F. The stroop color and word test. Front Psychol. 2017;12(8):557.
48 Neylan KD, Miller BL. New approaches to the treatment of frontotemporal dementia. Neurotherapeutics. 2023;20(4):1055–65. https://doi.org/10.1007/s13311-023-01380-6
49 Tan KS, Libon DJ, Rascovsky K, Grossman M, Xie SX. Differential longitudinal decline on the Mini-Mental State Examination in frontotemporal lobar degeneration and Alzheimer disease. Alzheimer Dis Assoc Disord. 2013;27(4):310–5. https://doi.org/10.1097/WAD.0b013e31827bdc6f
50 Leroy M, Bertoux M, Skrobala E, Mode E, Adnet-Bonte C, Le Ber I, et al. Characteristics and progression of patients with frontotemporal dementia in a regional memory clinic network. Alzheimers Res Ther. 2021;13(1):19. https://doi.org/10.1186/s13195-020-00753-9
51 Demurtas J, Schoene D, Torbahn G, Marengoni A, Grande G, Zou L, et al. Physical activity and exercise in mild cognitive impairment and dementia: an umbrella review of intervention and observational studies. J Am Med Dir Assoc. 2020;21(10):1415–22.e6. https://doi.org/10.1016/j.jamda.2020.08.031
52 Kumfor F, Piguet O. Disturbance of emotion processing in frontotemporal dementia: a synthesis of cognitive and neuroimaging findings. Neuropsychol Rev. 2012;22(3):280–97. https://doi.org/10.1007/s11065-012-9201-6