**Effects of neurobic exercise on cognitive function and serum brain-derived neurotrophic factor (BDNF) in the normal to mild cognitive impairment older people: a randomized control trial**

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Original Article

Effects of neurobic exercise on cognitive function and serum brain-derived neurotrophic factor (BDNF) in the normal to mild cognitive impairment older people: a randomized control trial

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Abstract

The purpose of this study was to examine the effects of neurobic exercise on cognitive function and serum BDNF in normal to mild cognitive impairment elderly. Fifty-one participants were simple randomized into two groups, the intervention group received one hour neurobic exercise training per session, for two sessions a week for 24 weeks and the control group engaged in their routine activities twice a week at senior club. All subjects were assessed by using a battery of neuropsychological tests and serum BDNF. The results showed that the experimental group had significantly improved cognitive scores when compared to the control group (p<0.05). Only in the experimental group, was there a significant increase in serum BDNF after completing neurobic exercise session. The study indicated that neurobic exercise has an effect on
cognitive function in aging. Moreover, increasing of serum BDNF level might be an indicator for the enhancement of brain function.

**Keyword:** neurobic exercise; cognitive function; serum brain-derived neurotrophic factor; normal to mild cognitive impairment, older people

1. **Introduction**

The prevalence of dementia is increasing and it is estimated to have 46.8 million people suffering with dementia worldwide in 2015. This number is expected to almost double every 20 years, reaching 74.7 million in 2030 and 131.5 million in 2050 (Alzheimer’s Disease International, 2015). **Dementia is a broad category of brain diseases where memory, thinking, behavior and the ability to perform daily activities severely deteriorates (WHO, 2017).** The proportionate increase in prevalence is expected to be much steeper in low and middle income countries, where half of new dementia cases are in Asia. According to the World Health Organization (WHO), development of preventative strategies for dementia is one of the research priorities to reduce the global burden of dementia by 2025 (World Health Organization, 2016). One approach to reduce the prevalence of dementia is to develop strategies to delay its onset in healthy individuals or in those at risk of developing dementia (Gates, Sachdev, Fiatarone-Singh, & Valenzuela, 2011). Cognitive stimulation and cognitive training intervention using a structured practice of complex mental activity in order to enhance cognitive function have been investigated and consistently show benefit in the cognitive function in people with mild to moderate dementia (Aguirre, Woods, Spector, & Orrell, 2013). Recent studies have explored the potential benefit of cognitive intervention in older people with mild cognitive impairment and subjective cognitive decline (Suzuki et
The findings demonstrated that cognitive enhancement is possible even when the subjects appear cognitively normal on standardized neuropsychological testing. People with mild cognitive impairment could learn new information and memory strategies. However, the limitation of previous studies are small sample size, limited details of randomization, lack of adequate controlled studies, heterogeneity of intervention and outcome measured, and lack of standardized instruments of measurement (Legault et al., 2011; Nouchi et al., 2012). Furthermore, studies of biomarkers to prove the improvement of neuropsychological tests by cognitive intervention are still limited.

The neurobic exercise is performed via the five physical senses of sight, hearing, smell, taste, and touch. Moreover, neurobic exercise can enhance the nerve impulse and interconnections among different data within the brain. In addition, neurobic exercise can stimulate neurons to create brain nutrients called neurotrophins which have a chemical effect on the growth of nerve cells and also have the effect of increasing the branching of nerve fibers, slowing the degeneration of nerve cells (Katz & Rubin, 1999). Neurobic exercise is generally an activity to do in everyday life but it is modified through a new experience such as blindness activities to modify the information from the senses (Katz & Rubin, 1999). A previous study was performed in 22 female dementia patients that demonstrated a better score in memory testing after the neurobic exercise. However, there was no control group and it was studied only in female subjects with dementia (Kanthamalee & Sripankaew, 2013). Generalizing to the general population needs further investigation to confirm this result in other groups of the population.
Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family of growth factors. It is expressed throughout the brain, particularly in the hippocampus, basal forebrain and prefrontal cortex which are essential for learning, memory and other cognitive functions (Pezawas et al., 2004). It has an effect on neurite outgrowth, synaptic plasticity (Rossi et al., 2006), neuronal survival (Husson et al., 2005), and neuronal differentiation (Lu, Pang, & Woo, 2005). The BDNF has benefits in long-term memory and overall brain function (Alonso et al., 2002). It has Tropomyosin-related kinase B (TrkB) as a signaling receptor. Several studies revealed its association with certain psychiatric and neurologic disorders. BDNF/TrkB signaling may be involved in Alzheimer’s disease (AD), and associated with amyloid β and tau which are neuropathologic hallmarks of AD (Zhang, Kang, Li, Xiao, & Zhou, 2012). Although platelet is a major source of peripheral BDNF, no significant difference was found between serum and plasma. Serum levels are influenced by platelets and plasma level results are inconsistent. Thus, serum measurements seem more reliable than plasma ones (Serra-Millàs, 2016). Peripheral BDNF has been proposed as a biomarker for the successful treatment of major depressive disorder (Polyakova et al., 2015). It could be a possible biomarker of cognitive function in AD as well. Previous research has demonstrated the increase of BDNF with a varied physical exercise program. However, the magnitude of this effect was lower in females compared to males (Szuhany et al., 2015).

With the increasing incidence of dementia, strategies to slow down the degeneration of the brain are vital. Neurobic exercise might stimulate the different parts of the brain and can be done in daily practice at home. Thus, establishing a new brain
fitness program, which uses the five physical senses is particularly interesting. Therefore, the researchers took daily activities that can be considered a new form of neurobic exercise. This research is a randomized controlled trial (RCT) aimed to study the effect of neurobic exercise on both cognitive function and biomarker-serum brain-derived neurotrophic factor (BDNF) in older people who were cognitively normal or had mild cognitive impairment. The aim was to find an alternative way to prevent cognitive decline or help to reduce a risk of dementia that may develop in the future.

However the evidence of the effects of neurobic exercise program was lacking, this research will be a supporting reference for further study on neurobic exercise in the future.

2. Materials and Methods

Participants

A single-blind (assessors blinded) RCT was conducted. The participants were 51 local community-dwelling non-demented older adults and adults with mild cognitive impairment who attended an elderly club or local center for older people in a province near Bangkok (Pathum Thani province). The inclusion criteria were 1) Aged between 60-80 years; 2) the Barthel Activities of Daily Living score was more than 12 points; 3) No history of psychiatric disorder or neurological condition (e.g., epilepsy, stroke, dementia, head injury, etc.); 4) No history of functional decline and independent in social and occupational activities; 5) Had normal physical senses; and 6) Fluent in Thai both speaking and writing. Exclusion criteria were those with 1) significant visual or hearing impairment; 2) previous neurological disorders; 3) current smoking or alcoholic
drinking; and/or 4) medical problems that could interfere with the attendance of the study session. The participants were withdrawn from the study if 1) they were not willing to continue the study; 2) they missed the program for more than 20% of the sessions or 4 consecutive sessions; and/or 3) they could not comply with the study protocol, such as having acute medical illness or injury. Before the intervention, every participant was informed about the study objectives and process and then, an informed consent was given. The study was approved by the ethics review committee for research involving human research subjects, Health Science Group, Chulalongkorn University.

The two groups were matched on age, and global cognitive status as measured by the Montreal Cognitive Assessment (MoCA) Thai version, and the Barthel Activities of Daily Living: (ADL) score. These participants were randomly assigned to either neurobic exercise program (NG) or usual care as a control group (CG).

From previous studies, the cognitive change after the intervention between groups varied from 23-98% (Gates et al., 2011; Suzuki et al., 2013). The sample size for this study was determined to compare cognitive measures based on the expected effect size of 40% and the standard deviation of the observations in each of the 2 groups at 70%. A sample size of 25 per group was required to detect change on the neuropsychological test, with 80% power and type I error at 5%. As there were 48 sessions of the study program, the researcher allowed a 30% dropout, 36 participants per group were required.

**Neuropsychological examination**

A neuropsychological testing performed twice: (1) baseline and (2) within 1–3 days after the last training session at the 24th week. A cognitive assessment was
performed to measure global cognitive function, attention, auditory and visual memory and executive function. The authors used The Montreal Cognitive Assessment (Nasreddine et al., 2005) in Thai version to measure general cognitive function. Trail making test A and B was used to measure attention (Reitan & Wolfson, 1985). The memory function was tested by Verbal Paired Associates I and II in Wechsler Memory Scale third edition: WMS-III to measure the auditory memory (Wechsler, 1997) and Rey-Osterrieth Complex Figure test to measure the visual memory (Osterrieth, 1945). The executive function was measured by the Wisconsin Card Sorting Test (Heaton, Chelune, Talley, Kay, & Curtiss, 1993). All tests were performed by an experienced neuropsychologist who was blinded to the study group.

**Neurobic Exercise Group (NG)**

Neurobic exercise applies five physical senses, i.e., sight, hearing, smelling, tasting, touching and feeling the emotion, in training exercise. Neurobic exercise comes from the scientific basis where the cerebral cortex consists of an unexpectedly vast number of different areas, and each area specializes in different functions to receive, render, and store information from the physical senses. Therefore, the cognition through the senses does not conclude in one place in the brain because there are hundreds of different neural pathways and a lot of connecting areas in the cerebral cortex. Neurobic exercise encourages the uses of this vast unused area in the brain to induce more interconnections and possible combinations of the brain (Katz & Rubin, 1999).

The developed neurobic training program consisted of nine exercises with five physical senses stimuli. The program was reviewed by senior clinicians and university
lecturers (1 psychiatrist, 2 psychologists, 1 neuropsychologist and 1 neurophysiologist). The Item Objective Congruence (IOC) was 0.82. Neurobic exercises program was as follows:

1) Draw and paint on the paper as instructed by the researcher within the time set,

2) Touch stuff inside the box, and allow the subjects to guess what they have touched. Ten minutes later, the participants were asked to write the answer on the paper with a non-dominant hand,

3) Play the word dumb game by using only gestures and speech,

4) Close eyes with a blindfold, smell an object (food, herb and flavoring) and guess what it was. Ten minutes later, the participants were asked to write the answer on the paper with a non-dominant hand,

5) Close eyes with a blindfold, listen to a sound and guess what it was. Ten minutes later, the participants were asked to write the answer on the paper with a non-dominant hand,

6) Close eyes with a blindfold, taste juice or food and guess what they ate or drank. Ten minutes later, the participants were asked to write the answer on the paper with a non-dominant hand,

7) Write based on a proposition with a non-dominant hand,

8) Mold clay within the time set,

9) Play a word guessing game by using a finger to write a word on the back of the other participant.
These training activities affected a widespread network of thalamic and bihemispheric structures in the frontal lobe which controlled attention (Filley, 2002) and also stimulated hippocampus which is a part of the limbic system affecting memory function. In addition, the training program also stimulated the prefrontal lobe affecting high brain resolution, planning and reasoning in decision making (Manchester, Priestley, & Jackson, 2004; Serino et al., 2006).

Each individual session consisted of three out of nine exercises, and lasted for one hour. The whole training protocol included one hour of cognitive training per day for two days per week during a period of 24 weeks (48 sessions). 2 days per week was minimum frequency of cognitive training that could improve cognitive function, while 24 weeks of intervention was an appropriated duration reported to have a significant improvement of cognitive function. (Bugos et al., 2007; Noice & Noice, 2009; Klusmann et al., 2010; Slegers, Boxtel, & Jolles, 2009).

Control Group (CG)

The control group was asked to attend seminar in weeks 6, 12 and 18. The seminar content was about health promotion for older people. The control group was engaged in their routine activities as usual twice a week at their senior club.
Serum BDNF measurement

Blood samples were collected twice: (1) baseline and (2) within 1–3 days after the last training session at the 24th week. Blood samples were collected between 8:00 and 9:00 a.m. into a free-anticoagulant vacuum tube. The samples were allowed to clot and then centrifuged at 1500 × g for 15 min. Serum parts were stored at −80 °C until they were assayed and thawed immediately prior to the measurement of biochemical parameters. Serum levels of BDNF were determined using enzyme-linked immunosorbent assay kits (Quantikine ELISA Human Free BDNF Kit, R&D Systems, Inc., Minneapolis, MN, USA).

3. Statistical analysis

Statistical analysis was performed using SPSS for Windows version 19 software. Baseline characteristics and characteristics of factors were analyzed using descriptive statistics. Categorical variables of gender, education, and physical activity and medical illness were analyzed using the Chi-squared test. The Fisher exact test was used in a count of less than 5. MoCA and Barthel ADL scores were determined by using the independent sample t-test. Within the group, cognitive function score and serum BDNF levels were determined by using the paired sample t-test. and between two groups using the independent sample t-test.
4. Results

*Demographic and clinical characteristics*

Seventy-two participants were included in the study. There were 21 participants who withdrew from this study (8 in NG and 13 in CG). In the NG group, the reasons for withdrawal were 1) duration of study was too long (4 cases); 2) acute medical illness (1 case); and 3) transportation problem (3 cases). In CG, all 13 cases dropped out because the duration of study was too long. The demographic characteristics of the 51 participants who completed the study are summarized in Table 1. Two groups were not significantly different in age, gender, medical illness, engagement in physical activities, psychotropic drug use, MoCA score and Barthel ADL score.

*Cognitive scores and serum BDNF levels*

The cognitive scores of neuropsychological evaluations and serum BDNF levels in the control and neurobic exercise groups before and after intervention are shown in Table 2. All parameters between CG and NG at baseline were not significantly different (p > 0.05).

Comparison between NG and CG for Rey-Osterrieth Complex Figure test T-score and the Wisconsin Card Sorting Test-Preservative response (T-score and Standard-score) were significantly higher in NG than in CG (p < 0.05). Regarding the Trail making test part B, NG had a significantly lower score than CG (p < 0.05).

In CG, the post-test score of the Wisconsin Card Sorting Test-Preservative response was significantly lower than the pretest score (p < 0.05).
The post-test scores of the Verbal Paired Associates I, Rey-Osterrieth Complex Figure test both immediate and delayed T-score and Wisconsin Card Sorting Test- Error response in the NG were significantly higher than the pretest (p < 0.05) (Table 2) and the Trail Making Test part B were significantly lower than the pretest (p < 0.05).

In addition, serum BDNF level in the NG was significantly higher than the pretest (p < 0.05) (Table 2, and Figure 1).

In NG, the positive percent change of the serum BDNF, TMT-B, VPA I, ROCFD, WCSTEs, ROCF I and WCSTEss were 29.73%, 22.84%, 12.38%, 11.40%, 10.29%, 10.23% and 6.82% respectively.

In CG, the negative percent change of the WCSTPts and WCSTPss were 10.11 and 6.69% (Table 2).

5. Discussion

In this study, we aimed to examine the effects of neurobic exercise on cognitive function and serum BDNF in cognitively normal to mild cognitively impaired elderly subjects. We found that neurobic exercise improved cognitive function in older adults. The participants who trained in the neurobic exercise program showed a significant increase in the score of the Rey-Osterrieth Complex Figure test both immediate and delayed T-score more than subjects who untrained in CG, which reflected that they had better visual memory. Kanthamalee and Sripankaew (2013) found that neurobic exercise improved 23% higher from baseline and that results was concordant to this study. Neurobic exercise may help activate the prefrontal association cortex part of the brain which is responsible for creating memory (working memory) and stimulating
hippocampus and limbic system for improving memory function. The findings supported recent research, indicating that memory was improved by cognitive training in older people (Gumther, Schafer, Holzner, & Kemmle, 2003; Klussmann et al., 2010; O’Dwyer, Burton, Pachana, & Brown, 2007).

In addition, participants in NG had significantly lower Trail Making Test part B scores than CG. This result indicated that, after a training exercise, participants could pay attention on any situation or event for a longer period. Mozolic, Long, Morgan, Rawley-Payne and Laurienti (2011) used the modality-specific attention training program to improve attention score by 25.89% from baseline which is consistent with our finding where the improvement was found by 27.84%. The neurobic exercise helps stimulate a widespread network of thalamic and bihemispheric structures in which the frontal lobes enhance attention ability in aging (Filley, 2002). Beneficial changes at structural and functional levels in the aging brain can also occur due to cognitive training (Lustig, Shah, Seidler, & Reuter-Lorenz, 2009). Moreover, previous studies support our results, indicating that attention ability was enhanced by cognitive exercise (Tusch et al., 2016).

We investigated the executive function by using the Wisconsin Card Sorting Test, and our results showed that both T-score and Standard-score of Wisconsin Card Sorting Test -Preservative response were significantly higher in NG than in CG where 12.99% and 8.93% improvements were found accordingly. These results indicated that the neurobic exercise helped improve mental flexibility in older adults implying that the participants could make rational decisions and solve problems better. The neurobic exercises might help stimulate brain activities in part of the prefrontal lobe involving
making decisions, solving complex problems and planning (Manchester et al., 2004; Mapou, 1992; Serino et al., 2006). The study supported that cognitive training can improve executive function in older people (Ball et al., 2002; O’Dwyer et al., 2007). After intervention of CG, we found that T-score and Standard-score of the Wisconsin Card Sorting Test-Preservative response were significantly lower than those of pre-test score by 10.11% and 6.69%, accordingly. These results indicate that older adults who do not receive the neurobic exercise or any brain training might have a decline in mental flexibility and executive function involving making decisions, solving complex problems and planning.

Finally, we examined serum BDNF level between NG and CG. The level of serum BDNF significantly increased after the intervention in NG showing that neurobic exercise induced higher serum BDNF which might reflect the enhancement of brain function. Angelucci et al. (2015) found that cognitive training improved the level of serum BDNF by 40% from the baseline which is consistent with our study. Generally, levels of BDNF relate to the health of the brain. Patients who have low levels of BDNF are more likely to have Alzheimer, depression, schizophrenia, and Huntington’s Disease (Ciammola et al., 2007; Gama et al., 2007; Laske et al., 2006; Piccinni et al., 2008). Increasing age was associated with smaller hippocampal volumes, reduced levels of serum BDNF, and poorer memory performance. Lower levels of BDNF were associated with smaller hippocampus and poorer memory, even when adjusting for the variation related to age (Erickson et al., 2010). Moreover, BDNF is a potential marker of neural integrity. In humans, BDNF is involved in the formation of long-term memory in the hippocampus (Yeh et al., 2012). The BDNF is an important molecular mediator of the
neuroplasticity of the brain, particularly in survival, differentiation and neuronal growth (McAllister, Katz, & Lo, 1999) and may influence brain functions, including learning and memory (Tyler, Alonso, Bramham, & Pozzo-Miller, 2002). Thus, the increase of BDNF might contribute to a reduction of dementia risk.

The strength of this study is that it includes older people with normal cognition or mild cognitive impairment who are the main proportion of this age group. Also, the tools and activities used in the intervention are easily integrated into other home-based activities. Successful intervention could be implemented in a large population. Also, with the significant increase of serum BDNF in the intervention group as a biomarker, it is a potential intervention to enhance brain function. In addition, the neuropsychological test was performed with an interval period of 24 weeks; therefore, the practice effect was unlikely to occur. Another concern regarding the neuropsychological testing is that it takes elderly long time to finish the test making them less attractive and easily lose focus.

In conclusion, this study indicates that neurobic exercise can increase the level of serum BDNF indicating enhancement of brain function. As a result, neurobic exercise can be used as an effective method to create a brain training program to reduce the risk of dementia in the elderly.
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References


in the dopaminergic pathway with memory in a healthy Chinese population.

*Brain and Cognition, 80*(2), 282-289. doi:10.1016/j.bandc.2012.06.005
### Table 1
Baseline demographic and clinical characteristics of participants in the control and neurobic exercise groups

<table>
<thead>
<tr>
<th>Data</th>
<th>Control (n=23)</th>
<th>Neurobic exercise (n=28)</th>
<th>p-value</th>
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<tr>
<td>Age; years (mean ± SD)</td>
<td>69.35±5.74</td>
<td>70.36±5.17</td>
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<td>Female (n,%)</td>
<td>11 (47.8%)</td>
<td>15 (53.6%)</td>
<td>0.683</td>
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<tr>
<td>Education (n, % secondary school and lower)</td>
<td>11 (47.8%)</td>
<td>13 (46.4%)</td>
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<td>Physical activity (n, % exercise less than once a week)</td>
<td>10 (43.5%)</td>
<td>13 (46.4%)</td>
<td>0.833</td>
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<td>Medical illness</td>
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<tr>
<td>• Hypertension</td>
<td>8 (34.8%)</td>
<td>11 (39.3%)</td>
<td>0.741</td>
</tr>
<tr>
<td>• Diabetes mellitus</td>
<td>5 (21.7%)</td>
<td>7 (25%)</td>
<td>0.785</td>
</tr>
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<td>• Dyslipidemia</td>
<td>4 (17.4%)</td>
<td>4 (14.3%)</td>
<td>0.990</td>
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<tr>
<td>• Cardiovascular diseases</td>
<td>1 (4.3%)</td>
<td>1 (3.6%)</td>
<td>0.990</td>
</tr>
<tr>
<td>• No known underlying disease</td>
<td>12 (52.2%)</td>
<td>13 (46.4%)</td>
<td>0.683</td>
</tr>
<tr>
<td>% psychotropic drug used (n, %)</td>
<td>0</td>
<td>0</td>
<td>NA</td>
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<td>MoCA (mean ± SD)</td>
<td>18.09 ± 5.03</td>
<td>20.54 ± 4.57</td>
<td>0.075</td>
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<td>Barthel ADL score (mean ± SD)</td>
<td>19.78 ± 1.04</td>
<td>19.43 ± 1.50</td>
<td>0.344</td>
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<td>Variables</td>
<td>Control (n=23)</td>
<td>Neurobic exercise (n=28)</td>
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<tr>
<td>-----------</td>
<td>----------------</td>
<td>-------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre-test Mean ± SD</td>
<td>Post-test Mean ± SD</td>
<td>Difference Mean (95% CI)</td>
</tr>
<tr>
<td>MoCA</td>
<td>18.09±5.03</td>
<td>18.26±6.58</td>
<td>0.17 (-1.78, 1.43)</td>
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<tr>
<td>VPA I</td>
<td>8.30±2.49</td>
<td>8.91±3.10</td>
<td>0.60 (-1.51, 0.30)</td>
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<tr>
<td>VPA II</td>
<td>8.57±2.66</td>
<td>8.78±2.62</td>
<td>0.21 (-1.08, 0.64)</td>
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<tr>
<td>ROCFI</td>
<td>38.78±14.47</td>
<td>39.70±15.94</td>
<td>0.91 (-6.00, 4.18)</td>
</tr>
<tr>
<td>ROCFD</td>
<td>37.17±14.62</td>
<td>37.52±16.36</td>
<td>0.34 (-6.31, 5.62)</td>
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<td>TMT-A</td>
<td>126.13±65.17</td>
<td>116.78±56.54</td>
<td>9.34 (-23.87, 42.56)</td>
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<tr>
<td>TMT-B</td>
<td>284.33±140.75</td>
<td>280.48±145.73</td>
<td>3.85 (-34.37, 42.09)</td>
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<tr>
<td>WCSTEts</td>
<td>34.30±8.32</td>
<td>34.17±7.27</td>
<td>0.13 (-2.66, 2.92)</td>
</tr>
<tr>
<td>WCSTEss</td>
<td>76.48±12.41</td>
<td>76.30±10.96</td>
<td>0.17 (-3.99, 4.33)</td>
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<tr>
<td>WCSTPts</td>
<td>37.39±8.14</td>
<td>33.61±8.20</td>
<td>3.78 (0.70, 6.86)</td>
</tr>
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<td>WCSTPss</td>
<td>80.96±11.98</td>
<td>75.54±12.15</td>
<td>5.39 (0.80, 9.98)</td>
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<td>WCSTCts</td>
<td>34.35±7.56</td>
<td>35.17±6.46</td>
<td>0.82 (-3.25, 1.60)</td>
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<td>WCSTCts</td>
<td>77.04±11.21</td>
<td>77.87±9.83</td>
<td>0.73 (-4.03, 2.55)</td>
</tr>
<tr>
<td>Serum BDNF</td>
<td>4853 ± 3266</td>
<td>6045 ± 3669</td>
<td>1193 (-352, 2737)</td>
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</table>
MoCA = Montreal Cognitive Assessment (score); VPA I = Verbal Paired Associates I (scale score); VPA II = Verbal Paired Associates II (scale score), ROCFI = Rey-Osterrieth Complex Figure Immediate (T-score); ROCFD = Rey-Osterrieth Complex Figure Delayed (T-score); TMT-A = Trail making test A (second); TMT-B = Trail making test B (second); WCSTEs = the Wisconsin Card Sorting Test Error response (T-score); WCSTEss = the Wisconsin Card Sorting Test Error response (Standard-score), WCSTPts = the Wisconsin Card Sorting Test-Preservative response (T-score); WCSTPss = the Wisconsin Card Sorting Test-Preservative response (Standard-score); WCSTCts = the Wisconsin Card Sorting Test-Conceptual response (T-score); WCSTCss = the Wisconsin Card Sorting Test-Conceptual response (Standard-score); Serum BDNF = Serum Brain-Derived Neurotrophic factor (pg/mL); CI= confidence interval.

* p < 0.05 (within group); † p < 0.05 (between two groups).

**Table 2** Cognitive tests and serum BDNF levels between the control and neurobic exercise groups, before and after intervention.
**Figure 1** Serum BDNF levels before and after the neurobic exercise compared with those of the control group. The plots are shown as mean ± SEM. An asterisk indicates a significant difference at p value < 0.05 using paired t-test.