■ ORIGINAL ARTICLES

Physical activity affects cognitive function in view of prefrontal cortex activation

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ABSTRACT: Previous studies have revealed that physical activity can affect brain function and cognitive decline. Additionally, we confirmed that brain activation in the prefrontal cortex (PFC) during a cognitive task was correlated with cognitive function. Based on these findings, we hypothesized that brain activation also affects cognitive function, which increases due to stimulation from physical activity. The purpose of this study was to verify causal relationships between physical activity, PFC activation, and cognitive function using the statistical method of path analyses in a multi-model approach.

Forty-six healthy volunteers (10 males, mean age: 76.1, standard deviation: 6.8) participated in this study. Informed consent was obtained from all participants prior to enrollment. This study was approved by the Ethics Committee of Seirei Christopher University (approval No. 10067). We assessed physical activity via participants' self-reports, determined PFC activation during a dual task using near-infrared spectroscopy, and measured cognitive function with the Trail-Making Test Part B. To determine the causal relationship between physical activity, PFC activation, and cognitive function, path analyses were conducted using AMOS 16 structural equation modeling.

The structural equation model was a good fit (root mean square error of approximation = 0.001). Several significant direct paths were identified: (1) from physical activity to PFC activation (b = 0.37), and (2) from PFC activation to cognitive function (b = 0.32).

This study statistically revealed the causal relationships between physical activity, PFC activation, and cognitive function. Path analyses indicated that physical activity affected cognitive function via PFC activation.

Key words: brain activation, cognitive function, physical activity

INTRODUCTION

Alzheimer's Disease International estimated that 36 million people worldwide are living with dementia, with numbers doubling every 20 years to 66 million by 2030, and 115 million by 2050[1]. The population is aging with ever-larger numbers of individuals reaching ages where a decline in function is more common. Therefore, preventing cognitive function decline and dementia is one of the most important issues worldwide.

Both cognitive function and brain volume decline with age. Age-related changes to the brain have been shown to occur earliest in the prefrontal cortex (PFC)[2,3], and Raz, et al.[4] have shown that the most substantial age-related decline in brain volume was found in the PFC. Age leads to a decline in the cerebral blood flow of the PFC[5,6]. Moreover, patients in the early stages of dementia have lower PFC blood flow than age-matched controls[7]. Kalpouzos, et al.[8] have shown that the decrease in glucose metabolism of the PFC was mostly related to aging in healthy elderly participants.

Therefore, maintaining PFC function is important for preventing cognitive decline. Many studies have clarified that certain life styles such as those involving physical activity[9-12], cognitive activity[13-15], and good eating habits[16-19] may be able to prevent cognitive impairment and dementia. In particular, the role of physical activity is supported by evidence from both behavioral and physiological studies.

Larson, et al.[10] indicated in a cohort study with a mean follow-up of 6.2 years that 158 out of 1740 participants developed dementia. The incidence rate of dementia was significantly lower in the group of participants who exercised three or more times per week compared to the group of participants who exercised less than three times per week. Lautenschlager, et al.[20] showed in a randomized trial that an intervention of at least 150 min of moderate-intensity physical activity per week provided a modest improvement in cognitive function. Moreover, brain-derived neurotrophic factor (BDNF) was related to Mini-Mental State Examination (MMSE) scores[21], which were decreased in patients with Alzheimer's disease[22], but increased after physical activity[23]. Therefore, physical activity is one of the most important lifestyles for preventing dementia or cognitive decline.

Previous studies have revealed that physical activity affects brain function or cognitive decline. Additionally, in a prior study[24], we confirmed that brain activation in the PFC during a cognitive task was correlated with cognitive function. Based on these findings, we formulated the hypothesis that brain activation also affects cognitive function, which increases due to stimulation by physical activity. However, these relationships have not yet been clarified. Therefore, the purpose of this study was to verify this hypothesis, and to identify the causal relationships between physical activity, brain activation, and cognitive function using the statistical method of path analyses in a multi-model approach.

SUBJECTS AND METHOD

Participants

Forty-six healthy volunteers (10 males and 36 females) participated in this study. All participants were healthy and without impairment in their visual or auditory senses. All participants demonstrated independence in activities of daily living. Informed consent was obtained from all participants prior to enrollment. This study was approved by the Ethics Committee of Seirei Christopher University (approval No. 10067).

Assessment of physical activity

We assessed self-reported physical activity by asking subjects whether they performed exercise as part of their normal routine[25]. Physical activities included walking for exercise, gardening or yard work, calisthenics or general exercise, bicycle riding, and swimming or water exercise. Minutes spent engaged in each of these activities were summed and expressed as min of activity/week[25]. This method of assessing physical activity is used in the field of public health[25,26], and its validity and reliability have been confirmed in previous studies[27,28].

Measurement of brain activation

We measured PFC activation during a dual task, in accordance with our previous study[24]. The dual task combined cognitive and motor execution tasks, which were performed while participants were seated. The cognitive task involved performing serial subtractions of 7 beginning with 100 and continuing as follows: 100, 93, 86, 79, etc. The results of each calculation were spoken aloud so accuracy could be assessed. In the motor execution task, seated participants were instructed to step in place with each foot. PFC activation was recorded using near-infrared spectroscopy (NIRS). Rest and task periods were each 30 s, and each task was repeated three times. During the rest period, participants counted aloud, each at their own pace.

The NIRS (ETG-7100, Hitachi Medical, Tokyo, Japan) measured the concentrations of oxygenated (oxy-Hb) and deoxygenated (deoxy-Hb) hemoglobin using two wavelengths of near-infrared light (695 nm and 830 nm). The distances between the injector and detector were 3.0 cm, and it was determined that the machine measured points in a shallow section of the gray matter, that is, the surface of the cerebral cortices[29,30]. The NIRS probes contained 3 × 10 lines of plastic transmitter/receiver shells (47 channels). We placed the optode grid on the head of the subjects according to the 10–20 positioning system and the lowest probes were placed along Fp1–Fp2 (Fig. 1). The sampling frequency was 10 Hz, the processed moving average was 5 s, a 0.5-Hz low-pass filter was used to remove the effects of Mayer waves, and a 0.01-Hz high-pass filter was used to remove baseline drift. Baseline corrections were made using the values from 10 s before the dual task and 20–30 s after the dual task using the least squares method. We only analyzed oxy-Hb signals as indicators of changes in regional cerebral blood flow because oxy-Hb is more sensitive than deoxy-Hb[29].

The task was repeated three times and the data were averaged. These analyses were performed using the "integral mode" of the ETG-7100 software (Hitachi Medical, Tokyo, Japan). The oxy-Hb data produced by the NIRS probes were segregated using a region of interest (ROI)[31], and included the probes focused on the PFC, which were isolated for analysis. The 14 channels (probe numbers 22, 23, 24, 25, 26, 32, 33, 34, 35, 41, 42, 43, 44, and 45) that corresponded to the PFC were selected as the ROI (Fig. 1). To confirm the task related changes (Δ oxy-Hb), we calculated the difference between the average values from the whole task period and the values from the 10-s rest period before the task.

Fig. 1. Near-infrared spectroscopy (NIRS) probe set-up

Measurement of cognitive function

The MMSE and Trail-Making Test (TMT) were used to assess participants' cognitive states. The MMSE is one of the most common screening tools for cognitive impairment in older adults[32], and it screens for impairment in overall brain function (i.e., the frontal, parietal, and temporal lobes)[33]. The TMT assesses several cognitive functions including working memory, attention, and motor speed[34,35]. The TMT consists of two parts, A and B. Performance on the TMT Part B (TMT-B) is thought to reflect PFC functions including executive functions, attention, and working memory[35,36]. Because we were specifically examining PFC activity and function, the TMT-B was administered to participants. The TMT-B contains the numbers 1 to 13 and Japanese characters scattered on a sheet of paper, and participants must draw a line alternately between consecutive numbers and the appropriate sequential Japanese character. The time required to complete the TMT-B task was measured for each participant.

Statistical analyses

To determine the relationships between physical activity, brain activation, and cognitive function, a path analysis was conducted using Structural Equation Modeling with IBM SPSS Amos (ver. 16.0 for Windows; IBM SPSS Japan, Tokyo, Japan). The mediating effects of the variables were evaluated in a specified model with path diagrams. Path analyses allow the testing of causal relationships among a set of observed variables. We constructed a model based on our hypothesis. We explored whether the TMT-B score could be a result of the brain activation and therefore, a cause for physical activity. To do this, we switched the positions of the TMT-B score, brain activation, and physical activity in the model. Moreover, cognitive function and brain activation were affected by aging[37,38]. We also used age to adjust each model. To compare the models, we examined the following standard fit indices: chi square (χ^2), comparative fit index (CFI), adjusted goodness-of-fit index (AGFI), root mean square error of approximation (RMSEA), and the Consistent Akaike Information Criterion (CAIC)[39-41]. The most frequently used goodness-of-fit index is χ^2, where a non-significant χ^2 implies a good fit of the model to the data. The CFI ranges between 0 and 1, with values larger than 0.90 indicating an adequate fit. The AGFI has a range between 0 and 1, with values larger than 0.85 indicating a good fit of the model. A RMSEA value below 0.05 indicates a close fit, and values over 0.10 represent a poor fit. The CAIC can be used to compare multiple models, with lower values indicating a better fit.

RESULTS

Participants' demographics and measurement scores are presented in Table 1. The participants (10 males and 36 females) ranged in age from 62 to 88 years (mean: 76.1, standard deviation [SD] 6.8). All participants had a score above 23 on the MMSE (mean score: 28.5, SD 1.7). The mean time required for the TMT-B was 150.9 s (SD 106.4).

Figure 2 shows our hypothesis model indicating that cognitive function is affected by physical activity via brain activation (Model 1). This model was a good fit and the following significant paths were identified: (1) from physical activity to brain activation, (2) from brain activation to cognitive function, and (3) from age to cognitive function.

We also verified another model (Model 2; Fig. 3), which was based on the hypothesis that brain activation is affected by physical activity and cognitive function. In this model, the path coefficients to brain activity from both physical activity and cognitive function were significant, respectively. However, the results of the fitting analyses indicated that the fit of Model 1 was better than Model 2 (Table 2).

Table 1. Participants' demographics and measurement scores

	Mean	SD	Median	Min	Max
Age (years)	76.1	6.8	78	62	88
Brain activation: Δ oxy-Hb (mm*Mm)	0.059	0.048	0.051	-0.015	0.186
Physical activity: physical activity per a week (min)	266.4	226.0	205	0	1050
Cognitive function: TMT-B score (s)	150.9	106.4	103.4	58.8	503.8
MMSE score	28.5	1.7	29	24	30

Abbreviations: MMSE, Mini-Mental State Examination; oxy-Hb, Oxygenated hemoglobin; SD, Standard deviation; TMT-B, Trail-Making Test Part B.

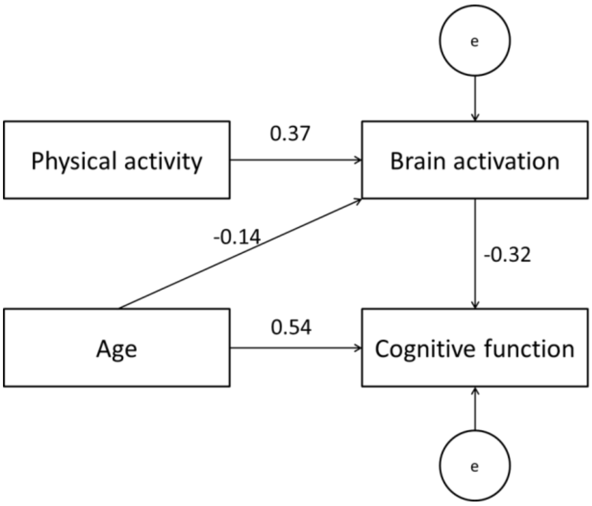

Fig. 2. Path analyses for hypothesized Model 1
Abbreviations: e, errors in variables.
Above each path is the path coefficient for that path. All standardized path coefficients, except for the one from age to brain activation, were statistically significant ($P < 0.05$).

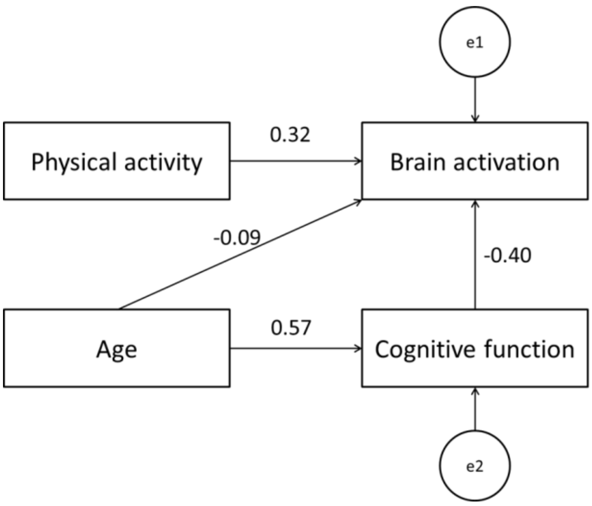

Fig. 3. Path analyses for hypothesized Model 2
Abbreviations: e, errors in variables.
Above each path is the path coefficient for that path. All standardized path coefficients, except for the one from age to brain activation, were statistically significant ($P < 0.05$).

Table 2. Fit indices of each model

	Model 1	Model 2
χ^2	0.04	1.23
CFI	1.00	0.99
AGFI	0.99	0.86
RMSEA	0.001	0.08
CAIC	43.45	44.71

All indices suggest Model 1 was a better fit than Model 2. Abbreviations: χ^2, chi square; CFI, comparative fit index; AGFI, adjusted goodness-of-fit index; RMSEA, root mean square error of approximation; CAIC, Consistent Akaike Information Criterion.

DISCUSSION

In this study, we examined the relationships between brain activation, physical activity, and cognitive function in older people using the statistical method of path analyses in a multi-model approach. The results demonstrated that Model 1 was the most statistically possible model. This model supported our hypothesis that cognitive functioning is affected by physical activity via brain activation.

The participants in this study all had MMSE scores above the commonly used cut-off score of 23[42]. However, some participants had lower TMT-B scores. Therefore, we considered that our group of participants contained some individuals with early cognitive decline, although their general cognitive functioning was maintained.

Our results revealed that PFC functioning as measured by the TMT-B was affected by the dual task combining cognitive and motor execution tasks. In order to perform the dual task, it is necessary to allocate attention properly to each cognitive and motor task. Therefore, the brain activation during the dual task might indicate an attentional function. Our prior study indicated a relationship between brain activation during the dual task and TMT-B scores. TMT-B scores reflect the attentional aspects of PFC functioning[34,35]. In the present study, we demonstrated that the path coefficient from brain activation during the dual task to the TMT-B score was significant. This means that cognitive function is affected by brain activation. Therefore, we clarified the causal correlation between cognitive function and brain activation, which suggests that cognitive functions depend on brain activation. To confirm this, we verified a second model, Model 2, in which brain activation was affected by cognitive function. In regard to Model 2, the path coefficient from cognitive function to brain activation was significant, but all fit indices (χ^2, CFI, AGFI, RMSEA, and CAIC) suggested that Model 2 was not better than Model 1. Therefore, Model 1 indicating that brain activation affects cognitive function appears to be more statistically probable than Model 2, and suggests that cognitive function affects brain function. Thus, our model implies that it might be effective to improve or maintain brain activation related to cognitive tasks in order to prevent cognitive decline.

The path coefficient from physical activity to brain activation was also significant. Participants in this study who had many hours of physical activity in a week had more brain activation during the dual task. In order for brain activation to occur during the task, the brain structure and brain blood vessels in the participant must be maintained because NIRS measures the blood flow at the brain surface. In previous studies, it has been suggested that physical activity has beneficial effects on brain structure and function. Colcombe, et al.[43] and Erickson, et al.[44] indicated that aerobic exercise training increases gray and white matter volume in the PFC. Bullitt, et al.[45] investigated the age-related changes in brain blood vessels, and suggested that by keeping a healthy state, exercise can increase the number of small-caliber brain blood vessels. Rosano, et al.[46] indicated that a group of participants who walked regularly for exercise had significantly greater PFC functioning and higher PFC activity than a control group. Many studies have indicated that physical activity in daily living has a beneficial effect on brain structure, and the results of this study showing that physical activity affects brain activation support these previous studies. Therefore, in the participants who engaged in physical activity regularly, the brain structure and blood vessels might have been kept in better condition, thus improving their brain activity.

Furthermore, physical activity has beneficial effects on cognitive function. Many studies have reported that aerobic exercise prevents cognitive decline[9-11]. Moreover, recent reports have suggested that both aerobic exercise and a higher level of total daily physical activity can help prevent cognitive decline[25,47]. In our results, we showed that Model 1, indicating physical activity affects cognitive function via brain activation, was a good fit. This suggests that physical activity has a beneficial effect on cognitive function via encouraging brain activation. A previous study reported the beneficial effects of physical activity on brain structure and cognitive function, respectively. However, these causal relationships were not clear. In the present study, we clarified the causal relationships between them statistically. This result encourages increasing the time spent engaging in physical activities in daily living to prevent cognitive decline and brain aging.

There were some limitations in this study. First, this study is only a cross-sectional study; therefore, it cannot indicate the real causal relationship. We intend to confirm it in a randomized control trial in a further study. Second, a physically active lifestyle is not the only method for preventing cognitive decline. Previous studies have shown that many other lifestyles including those with increased cognitive activities[13-15] or eating habits[16-19] can also prevent cognitive decline. Additionally, brain activity demonstrates sex-related differences[48]. We could not verify these differences because our sample size was too small. More studies with a larger number of participants and more detailed lifestyle evaluations are needed to confirm the sex differences and identify which lifestyle is the most beneficial for preventing cognitive decline and brain aging. Third, we could not investigate whole-brain activation because of the instrumental limitations. Therefore, future studies should examine whole-brain activation using other instruments and consider the connectivity between various regions of brain activation.

CONCLUSION

In conclusion, we revealed a causal relationship between physical activity, brain activation, and cognitive function by using a multi-model statistical approach with path analyses. The model in which cognitive function was affected by physical activity via brain activation was statistically reasonable. Physical activity might enhance task-related brain activation, and high brain activation might be beneficial when performing a cognitive task. This result suggests that regular physical activity may maintain or promote brain function and cognitive function. Therefore, encouraging physical activity may help decrease dementia.

REFERENCES

1) Batsch NL, Mittelman MS: World Alzheimer Report 2012 –Overcoming the stigma of dementia- Alzheimer's Disease International, London, pp.8-10,2012.
2) Sato K, Taki Y, Fukuda H, et al.: Neuroanatomical database of normal Japanese brains. Neural Netw 16:1301-1310,2003.
3) Smith EE, Jonides J: Storage and executive processes in the frontal lobes. Science 283:1657-1661,1999.
4) Raz N, Gunning FM, Head D, et al.: Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. Cereb Cortex 7:268-282,1997.
5) Bentourkia M, Bol A, Ivanoiu A, et al.: Comparison of regional cerebral blood flow and glucose metabolism in the normal brain: effect of aging. J Neurol Sci 181:19-28,2000.
6) Meltzer C, Cantwell M, Greer P, et al.: Does cerebral blood flow decline in healthy aging? A PET study with partial-volume correction. J Nucl Med 41:1842-1848,2000.
7) Imran MB, Kawashima R, Awata S, et al.: Parametric mapping of cerebral blood flow deficits in Alzheimer's disease: a SPECT study using HMPAO and image standardization technique. J Nucl Med 40:244-249,1999.
8) Kalpouzos G, Chételat G, Baron JC, et al.: Voxel-based mapping of brain gray matter volume and glucose metabolism profiles in normal aging. Neurobiol Aging 30:112-124,2009.
9) Barnes DE, Whitmer RA,Yaffe K: Physical activity and dementia: The need for prevention trials. Exerc Sport Sci Rev 35:24-29,2007.
10) Larson EB, Wang L, Bowen JD, et al.: Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med

144:73-81,2006.
11) Laurin D, Verreault R, Lindsay J, et al.: Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch Neurol 58:498-504,2001.
12) Morgan GS, Gallacher J, Bayer A, et al.: Physical activity in middle-age and dementia in later life: findings from a prospective cohort of men in caerphilly, South wales and a meta-analysis. J Alzheimers Dis 31:569-580,2012.
13) Akbaraly TN, Portet F, Fustinoni S, et al.: Leisure activities and the risk of dementia in the elderly: results from the Three-City Study. Neurology 73:854-861,2009.
14) Hall CB, Lipton RB, Sliwinski M, et al.: Cognitive activities delay onset of memory decline in persons who develop dementia. Neurology 73: 356-361, 2009.
15) Wilson RS, Barnes LL, Aggarwal NT, et al.: Cognitive activity and the cognitive morbidity of Alzheimer disease. Neurology 75:990-996,2010.
16) Barberger-Gateau P, Letenneur L, Deschamps V, et al.: Fish, meat, and risk of dementia: cohort study. BMJ 325:932-933,2002.
17) Li F-J, Shen L,Ji H-F: Dietary intakes of vitamin E, vitamin C, and β-carotene and risk of Alzheimer's disease: A meta-analysis. J Alzheimers Dis 31:253-258,2012.
18) Okereke OI, Rosner BA, Kim DH, et al.: Dietary fat types and 4-year cognitive change in community-dwelling older women. Ann Neurol 72:124-134,2012.
19) Peters R, Peters J, Warner J, et al.: Alcohol, dementia and cognitive decline in the elderly: a systematic review. Age Ageing 37:505-512,2008.
20) Lautenschlager NT, Cox KL, Flicker L, et al.: Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease. JAMA 300:1027-1037,2008.
21) Laske C, Stransky E, Leyhe T, et al.: Stage-dependent BDNF serum concentrations in Alzheimer's disease. J Neural Transm 113:1217-1224,2006.
22) Phillips HS, Hains JM, Armanini M, et al.: BDNF mRNA is decreased in the hippocampus of individuals with Alzheimer's disease. Neuron 7:695-702,1991.
23) Cotman CW, Engesser-Cesar C: Exercise enhances and protects brain function. Exerc Sport Sci Rev 30:75-79,2002.
24) Ohsugi H, Ohgi S, Shigemori K, et al.: Differences in dual-task performance and prefrontal cortex activation between younger and older adults. BMC Neurosci 14:10,2013.
25) Buchman AS, Boyle PA, Yu L, et al.: Total daily physical activity and the risk of AD and cognitive decline in older adults. Neurology 78:1323-1329,2012.
26) Booth ML, Owen N, Bauman A, et al.: Social-cognitive and perceived environment influences associated with physical activity in older Australians. Prev Med 31:15-22,2000.
27) Ainsworth BE, Jacobs DR, Jr., Leon AS: Validity and reliability of self-reported physical activity status: the Lipid Research Clinics questionnaire. Med Sci Sports Exerc 25:92-98,1993.
28) Rauh MJ, Hovell MF, Hofstetter CR, et al.: Reliability and validity of self-reported physical activity in Latinos. Int J Epidemiol 21:966-971,1992.
29) Hoshi Y, Kobayashi N,Tamura M: Interpretation of near-infrared spectroscopy signals: a study with a newly developed perfused rat brain model. J Appl Physiol 90:1657-1662,2001.
30) Tamura M, Hoshi Y,Okada F: Localized near-infrared spectroscopy and functional optical imaging of brain activity. Philos Trans R Soc Lond B Biol Sci 352:737-742,1997.
31) Honda N, Matuoka T, Sawada Y, et al.:

Reorganization of sensorimotor function after functional hemispherectomy studied using near-infrared spectroscopy. Pediatr Neurosurg 46:313-317,2010.
32) Shigemori K, Ohgi S, Okuyama E, et al.: The factorial structure of the Mini-Mental State Examination (MMSE) in Japanese dementia patients. BMC Geriatr 10:36,2010.
33) Folstein M: Mini-mental and son. Int J Geriatr Psyhiatry 13:290-294,1998.
34) Kortte KB, Horner MD, Windham WK: The trail making test, part B: cognitive flexibility or ability to maintain set? Appl Neuropsychol 9:106-109,2002.
35) Stuss DT, Levine B: Adult clinical neuropsychology: lessons from studies of the frontal lobes. Annu Rev Psychol 53:401-433,2002.
36) Zakzanis KK, Mraz R, Graham SJ: An fMRI study of the Trail Making Test. Neuropsychologia 43:1878-1886,2005.
37) Ardila A, Ostrosky-Solis F, Rosselli M, et al.: Age-related cognitive decline during normal aging: the complex effect of education. Arch Clin Neuropsychol 15:495-513,2000.
38) O'Sullivan M, Jones D, Summers P, et al.: Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. Neurology 57,632-638,2000.
39) Browne MW, Cudeck R, Bollen KA, et al.: Alternative ways of assessing model fit. Sociol Methods Res 21:230-258,1992.
40) Burnham KP, Anderson DR, Huyvaert KP: AIC model selection and multimodel inference in behavioral ecology: some background, observations, and comparisons. Behav Ecol Sociobiol 65:23-35,2011.
41) Byrne BM: Testing for multigroup invariance using AMOS graphics: A road less traveled. Structural Equation Modeling 11:272-300,2004.
42) Braekhus A, Laake K,Engedal K: The Mini-Mental State Examination: identifying the most efficient variables for detecting cognitive impairment in the elderly. J Am Geriatr soc 40(11):1139-1145,1992.
43) Colcombe SJ, Erickson KI, Scalf PE, et al.: Aerobic exercise training increases brain volume in aging humans. J Gerontol A Biol Sci Sci 61:1166-1170,2006.
44) Erickson K, Raji C, Lopez O, et al.: Physical activity predicts gray matter volume in late adulthood The Cardiovascular Health Study. Neurology 75:1415-1422,2010.
45) Bullitt E, Rahman F, Smith J, et al.: The effect of exercise on the cerebral vasculature of healthy aged subjects as visualized by MR angiography. American Journal of Neuroradiology 30:1857-1863,2009.
46) Rosano C, Venkatraman VK, Guralnik J, et al.: Psychomotor speed and functional brain MRI 2 years after completing a physical activity treatment. J Gerontol A Biol Sci Sci 65:639-647,2010.
47) Middleton LE, Manini TM, Simonsick EM, et al.: Activity energy expenditure and incident cognitive impairment in older adults. Arch Intern Med 25:1251-1257,2011.
48) Jausovec N,Jausovec K: Resting brain activity: differences between genders. Neuropsychologia 48:3918-3925,2010.