Title:

Intermittent Hypoxia improves Cognitive Performance and Quality of Life in Elderly Adults

Authors' names:

PhD Lutz Schega, **PhD** Beate Peter, Alexander Toerpel, Harry Mutschler, **PhD** Berend Isermann, Dennis Hamacher

Institute where the work was conducted:

Department of Sport Science, Otto-von-Guericke-University Magdeburg, Germany

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Address of the corresponding author:

PhD Lutz Schega

Department of Sport Science, Otto-von-Guericke-University Magdeburg

Brandenburger Str. 9, 39104 Magdeburg, Germany

E-mail address: Schega.Lutz@ovgu.de

Tel.: +49 3916756126

Fax: +49 3916756754

Abstract

Background: Physical exercise has a positive effect on cognitive performance and quality of life. One reason for this is the upregulation of brain-derived-neurotrophic factor, which improves brain plasticity. Intermittent hypoxia promotes first, the proliferation of endogenous neuroprogenitors which leads to an increased number of newborn neurons and second, the expression of brain-derived-neurotrophic factor in the adult hippocampus. Intermittent hypoxia may, thus, support synaptic plasticity, process of learning and provoke antidepressant-like effects. Hence, intermittent hypoxia might also lead to improved cognitive functioning and quality of life.

Objective: This study aims to evaluate whether and to what extent physical activity with preceded intermittent hypoxic training is more effective than solely strength-endurance training on cognitive performance and quality of life.

Methods: Thirty-four elderly people were assigned to a control group or intervention group. Contrarily to the control group, the intervention group was supplied with an intermittent hypoxic training prior to a strength-endurance exercise program. In a pre-test and post-test, we examined the d2-test and the Number Combination Test as measures of cognitive performance. Moreover, we assessed quality of life with the Medical Outcomes Study Short-Form 36-Item Health Survey and Pittsburgh Sleep Quality Index.

Results: In the d2-test, the total number of processed symbols was larger for both groups in the post-test as compared to the pre-test. The number of correctly marked items minus error of confusion only showed an improvement in the intervention group. Our data of the Number Combination Test revealed that both groups performed faster in the post-test. After the treatment, the intervention group yielded higher scores in the Mental Component Summary as compared to the control group. In the post-test, the intervention group scored significantly better than the control group in the Pittsburgh Sleep Quality Index.

Conclusion: The data of the current study suggest that an additional intermittent hypoxic training combined with physical exercise augments the positive effects on cognitive performance in elderly humans. Intermittent hypoxia might also be able to improve quality of life.

Introduction

In gerontology, research frequently aims to discover efficient interventions that ensure the maintenance of psychological and physical activities. According to meta-analyses, physical fitness and exercise have either a small positive effect [1,2] or a modest positive effect [3] upon cognitive performance in humans. Animal studies indicated that metabolic [4] and neurochemical [5] functioning improves with enhanced aerobic fitness. Data of Kramer and co-workers [6] demonstrate that executive control processes supported by prefrontal and frontal cortex regions are sensitive to aerobic exercise in 60 to 75 years old individuals and a study by Lustig and co-workers [7] proved an increase in human hippocampus volume after chronic physical activity. In line with this, there is a decent body of evidence showing that physical exercise enhances the expression of brain-derived-neurotrophic factor (BDNF) in the brain and the blood [8-11]. Furthermore, Gunstad and co-workers [12] found that BDNF concentration in blood serum is positively correlated with the cognitive functioning in healthy older adults and Gomez-Pinilla [13] showed that the positive effects of exercise on cognition are substantially coupled with the availability of BDNF in the hippocampus. Therefore, it is most likely that exercise improves cognitive functioning performance. In addition, experiments in rats revealed that intermittent hypoxia (IH) promotes first, the proliferation of endogenous neuroprogenitors which leads to an increased number of newborn neurons and second, the expression of BDNF in the adult hippocampus [14]. As BDNF supports synaptic plasticity and process of learning [15] IH might lead to improved cognitive functioning. IH also provokes neurogenic antidepressant-like effects which might involve BDNF signaling [14].

Thus, besides cognitive functioning IH could also improve quality of life similar to antidepressants. Given that physical activity and fitness training enhance quality of life as well [16-18], we assume that both IH and physical activity help enhance first, cognitive performance and second, quality of life.

As per the results of above mentioned meta-analyses, physical fitness has only a small [1,2] or modest [3] effect on cognitive performance. However, we believe that IH training prior to a physical fitness intervention would amplify the positive effects on cognitive functioning. Furthermore, we think that this phenomenon might also occur in the case of quality of life. The aim of the present study was twofold: On the one hand we wanted to corroborate existing literature with respect to existing effectiveness of physical exercise on cognitive performance. On the other hand, we aimed to evaluate whether and (if applicable) to what extent strength-endurance training with a preceded intermittent hypoxic training is more effective than solely strength-endurance training on cognitive performance and quality of life. We hypothesized that an additional hypoxic training to a strength-endurance intervention would augment the effect sizes in measures of both cognitive performance and quality of life.

Methods

Participants

Thirty-four healthy but physically inactive subjects who were between 59 and 70 years of age were included in the experiment (please see Tab. 1 for subjects' anthropometric data). After signing a written informed consent, participants were randomly assigned to either the hypoxia group (HG) or the control group (CG). Both groups did not differ significantly in gender, age, height, weight and body mass index. The permission to conduct this study has been granted by the ethical committee of the Otto von Guericke University Magdeburg.

Please insert Tab. 1 around here

Cognitive testing

Neuropsychological performance of the participants was first assessed in the area of attention and concentration using the Mini Mental State Examination (MMSE; [19]) as well as the d2-test [20], and second in speed of cognitive performance using the Number Combination Test (Zahlen-Verbindungs-Test (ZVT); [21]).

We assessed the MMSE to screen for severe cognitive impairments in order to eliminate possible confounders. MMSE samples functions including arithmetic, memory and orientation [19].

The d2-test is a pencil-and-paper test containing 14 lines of 47 randomly assigned letters of "p" or "d". Each letter is accompanied by 0 to 4 dashes that are arranged without any order but above and/or below the letters. The participants were asked to mark the letter "d" accompanied with exactly 2 dashes in each line with a time constraint of 20 seconds per line. After the first 20 seconds the subjects switched to the second line performing the same task until they had finished also the 14th line. In that manner, the d2-test is ought to assess the capacity to focus on one stimulus besides suppressing attentiveness to other distractors. To be able to distinguish the orthographically similar letters "p" and "d" and simultaneously to identify the right amount of dashes, selective attention is also mandatory [22]. The reliability and validity of the d2-test is high for all parameters [23]. The total amount of processed symbols in the test (GZ) and the number of correctly marked items minus error of confusion (SKL) were computed. While GZ is a measure of working speed the SKL value is used as a measure of concentration and is interpreted as independent from adulteration and hence an objective measure to mirror attention span [23].

The ZVT determines speed of cognitive performance [21]. Basically, ZVT is a trial-making test which is composed of 4 parallel subtests (A-D), each representing a single trial. Here, the subjects were asked to combine 90 unordered numbers on one page as fast as they can. The time needed was measured for each trial and the mean time of all 4 trials represented the outcome measure. The validity and reliability have positively been tested [24].

Evaluation of quality of life

To assess quality of life, the participants completed 2 questionnaires. In the first form, they were instructed to complete the Medical Outcomes Study Short-Form 36-Item Health Survey (SF 12) which is a self-completed quantity of health related quality of life. This questionnaire comprises 8 domains covering physical functioning, vitality, role-physical, social functioning, bodily pain, role-emotional, general health and mental health (Lyons et al., 1994). Furthermore, there are two summary scores which summarize two domains: First, the Mental Component Summary and second, the Physical Component Summary. The internal consistency of the SF 12 is high [25].

As a second measure of quality of life, we assessed the subjects' reported sleep status in the past four months using the Pittsburgh Sleep Quality Index (PSQI). This test investigates the personal ascription of poor sleep. The questionnaire queries nine possible aspects for sleep disturbances. Furthermore, it retrieves abnormal sleep that provokes difficulties of functional performances [26]. The more often these symptoms arose the higher were the scores which indicate worse sleep quality. The PSQI is reliable even in elderly people [27].

Treatment procedure

During six weeks, HG received IH training. In three sessions per week, with one sessions lasting 1 hour, participants were asked to breathe intermittently a hypoxic air mixture (10 minutes) and normoxia (5 minutes). Afterwards, the subjects undertook a full body strength-endurance training program which lasted 30 minutes. Oxygen-reduced air was supplied via face-masks and hypoxia generators (Hypoxico EVEREST SUMIT II). All subjects in HG were provided with the same oxygen saturation. In the first two weeks, we adjusted the oxygen saturation to 90 %. In the third week, it was decreased to 85 %. Thereafter, the subjects were provided with 80 % of oxygen saturation for the remaining three weeks. CG undertook the same treatment. However, they were supplied with an air mixture that provoked an oxygen saturation of 94-98 %.

Statistical analysis

After testing on normal distribution (Kolmogorov–Smirnov-Test), all data were analyzed with t-tests for independent measures (HG vs. CG), t-tests for dependent measures (pre-test vs. post-test) and repeated measures ANOVA (with factors time x group) using a statistical computer program (IBM SPSS Statistics 20). The level of significance was set to $\alpha = .05$. From parameters which showed significant differences from pre-test to post-test, Cohen's d was calculated as a measure of effect size. Cohen [28] classified effect sizes into categories, with d = 0.2 as small, d = 0.5 as medium and d = 0.8 as large.

Results

Measures of cognitive performance

All subjects included in the experiment scored more than 27 points in the MMSE and both groups' performances were similar in pre-test and post-test. Regarding the d2-test, the total number of processed symbols (GZ) was larger for both groups in the post-test as compared to the pre-test (Fig. 1: B). A time x group effect has been observed (p = .040). The results of SKL which, denotes a measure of attention, showed a significant improvement from pre-test to post-test only in HG (Fig. 1: A). Here, an interaction effect (group x time; p = .034) has been found. Speed of cognitive performance was measured using ZVT. Our data show that both groups performed faster in the post-test as compared to the pre-test but any interaction effect was discovered (Fig. 1: C).

Insert Fig. 1 around here

Among all parameters that showed significant differences from pre-test to post-test SKL and GZ outcomes of HG produced the highest effects (d = 0.78 and 0.79 respectively). The effect size of GZ in CG was somewhat lesser (d = 0.40) as compared to HG. The results of ZVT depicted a larger effect in CG than in HG (d = 0.73 and 0.59 respectively).

Measures of Quality of Life

While the Physical Component Summary scores (SF 12) did not significantly differentiate groups nor differences have been observed comparing pre-test and post-test, the Mental Component Summary yielded higher scores after the intervention only in HG (Fig. 2: A & B). Here, an interaction effect just failed to become statistically significant (p = .058). Furthermore, we determined sleep quality with the PSQI. In the post-test, HG scored significantly higher than CG (Fig. 2: C).

Insert Fig. 2 around here

Regarding measures of quality of life, only HC improved significantly in the Mental Component Summary score and PSQI score. With d = 0.79 and d = 0.59 respectively, both scores showed relatively high effects.

Discussion

The purpose of our study was to investigate the effects of an additional intermittent hypoxic training prior to strength-endurance exercise on cognitive performance and quality of life in a healthy elderly cohort. Cognitively intact (MMSE > 27) healthy elderly individuals undertook either hypoxic training or breathed a placebo air mixture prior to a 30 minutes strength-endurance training. In pre-tests and post-tests, each participant performed the d2-test, ZVT-test, PSQI, MMST and SF 12 in order to measure cognitive performance and quality of life.

The notion that physical activity may have a positive effect on cognitive performance is commonly accepted. This possible effect can best be explained by two theories established in the literature. The first theory deals with structural changes in the brain. Exercise stimulates new blood vessels growth in the prefrontal cortex [29] and cerebellum [4] which presumably causes greater density of blood vessels in exercising animals as compared to control animals [4]. As the cerebellum-prefrontal-connection is responsible for coordinating thoughts, attentions and emotions, it certainly plays a role in the performance of cognitive tasks and it eventually affects the status of quality of life. The second theory, which might explain positive effects of physical activity on cognitive performance, is about the influence of exercise on expressing brain neurotransmitters. Hippocampal BDNF, for example, supports synaptic plasticity and process of learning [15].

Severe levels of oxygen desaturation are associated with neurocognitive morbidity [30,31]. However, mild hypoxic training is not only is innocuous [32], but mild hypoxic preconditioning has also a protective effect on neural viability of vulnerable hippocampal cells [33]. Furthermore, mild IH is ought to enhance cognitive performance [14].

Regarding the speed of cognitive performance (ZVT), we found that both HG and CG improved in the post-test which confirms the overall opinion of the literature [3]. An additional hypoxic training to strength-endurance exercise, however, did not show an amplifying effect. Though we did not find the expected interaction effect, we don’t believe that IH necessarily would not be effective regarding speed of cognitive processing. We rather speculate that a relative small effect caused by IH is probably superimposed by a relatively large effect caused by exercise on cognitive performance [3]. This is possibly due to new blood vessels growth in the prefrontal cortex which is actively involved in both cognitive activity and motor control [29].

As expected, our data shows that IH provokes an improvement in the measures of attentiveness (SKL and GZ see Fig 1: A & B). However, SKL did not significantly improve in CG. The time x group interaction effect indicates that the performance of HG vs. CG developed differently. Contrarily to HG, CG did not improve. There are two possible explanations. First, this might be due to the relative short time of the intervention period, as training programs lasting longer than six months are more effective in enhancing cognitive performance than shorter training periods between one and three months [34]. Second, this might be due to the reduced BDNF expression that IH produces presumably not only in rats [14] but probably also in humans, as BDNF actively modulates synaptic transmission and plasticity [15,35-37]. GZ, however, showed the anticipated results. Both groups yielded better scores in the post-test as compared to the pre-test. As, in addition, also a group x time interaction effect was observed, we conclude that the additional hypoxia training in HG caused the augmented effect. We assume that the effect caused by IH was added to the already existing effect of physical activity we observed in CG. The presence of larger effect sizes in HG as compared to CG supports our assumption.

In the same manner, the SF 12 Mental Component Score (see Fig. 2: A & B) and PQSI (Fig. 2: C) improved only in HG indicating that mild intermittent hypoxia is affecting both quality of life and sleep quality. Unexpectedly, CG did not improve. We anticipated that solely the strength-endurance treatment would show an effect. However, our data does not corroborate results from a study by Reid and co-workers [17] which also tested SF 12 and PSQI proved that aerobic exercise is effective in enlarging quality of life and sleep quality in older adults with insomnia. However, Reid and co-workers' [17] intervention period lasted 16 weeks which is more than three times longer than our treatment took. Furthermore, different results might be caused by different cohorts (healthy older subjects vs. older people with insomnia) and different treatment intensity (aerobic training vs. strength-endurance training). Regarding the positive effect of IH on HG we may assume that a potential BDNF expression might also have caused larger quality of life as it is known that induced hypoxia has antidepressant-like effects [14].

We did not assess levels of possible depression using a measure such as the Geriatric Depression Scale which is recommended to avoid confounders for research dealing with exercise and cognitive aging [38]. However, the predictive validity of SF-36 Mental Component Summary scores in screening for depressive disorder in older people has been positively tested [39] and in our subjects the outcome of SF 12 (which is the short form of SF 36) of all participants suggests that none of them was suffering from depression. Furthermore, we may have to acknowledge that different cognitive stimulation might mediate the effect of exercise on cognitive performance [38].

Taken together, our data mostly corroborate the existing literature which proved that physical exercise improves cognitive performance and quality of life. To the best of our knowledge, the current study provides the first data set which indicates that an additional IH training combined with physical exercise augments the positive effects on cognitive performance in elderly humans. From an application stand point, we carefully speculate that due to IH's possible ability to increase cognitive performance and quality of life, it might also be an effective preventive measure for elderly people prone to diseases like dementia and depression respectively. However, further research that proves our speculations is recommended.

Table headlines:

Tab. 1: Anthropometric data of included subjects (HG = Hypoxia Group, CG = Control Group).

Figure Legends:

Fig. 1: A: d2-SKL (the standardized number of correct responses minus errors of confusion); B: d2-GZ (the total number of worked symbols within the d2-test - a quantitative measure of the working speed); C: ZVT (the average time to solve the test)

Fig. 2: A: SF-12 Mental component score; B: SF-12 Physical component score; C: PSQI (Mean and standards deviations for subjective sleep quality; Low values denote higher sleep quality. T-tests for independent measures indicate a statistical significant improvement of the sleep quality for HG as compared to CG.)

Table 1:

Group	Gender	Age [years]		Height [cm]		Weight [kg]		BMI	
HG (N=17)	Women n = 13 Men n = 4	63,7 ± 3,4	p = 1.000	165,2 ± 5,3	p = .960	75,8 ± 13,3	p = .760	27,34 ± 5,0	p = .701
KG (N=17)	Women n = 13 Men n = 4	63,6 ± 3,2		165,4 ± 7,9		74,4 ± 12,6		27,58 ± 4,3	

Figure 1:

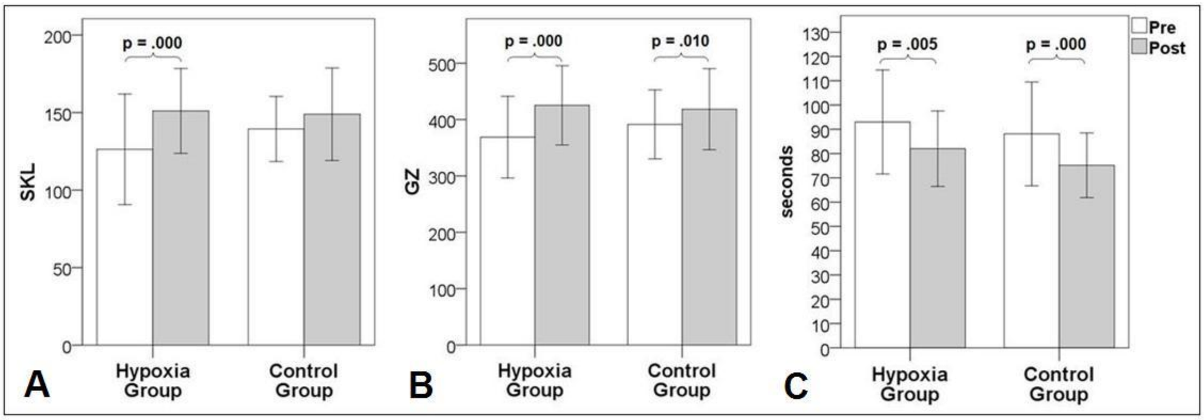
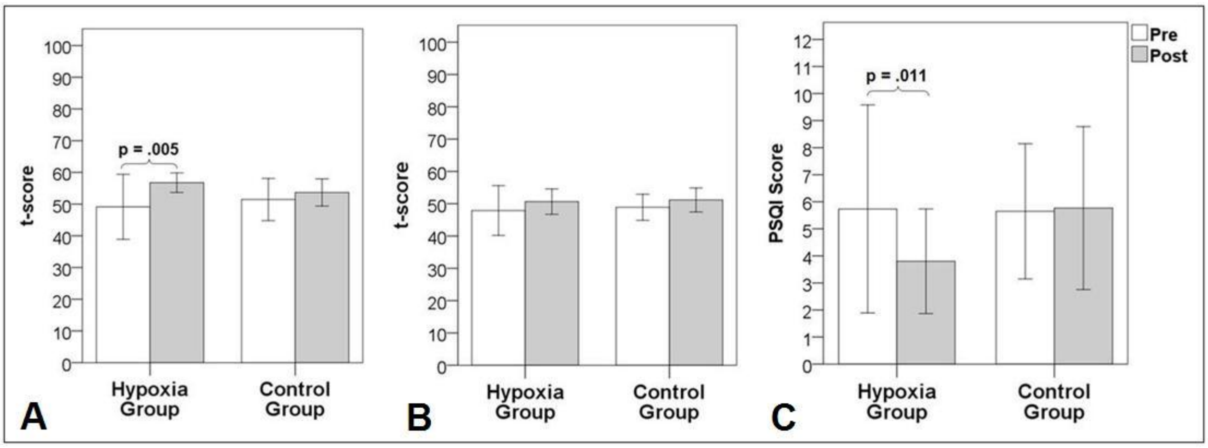


Figure 2:



References

1 Etnier JL, Salazar W, Landers DM, Petruzzello SJ, Han M, Nowell P: The influence of physical fitness and exercise upon cognitive functioning: A meta-analysis. Journal of Sport and Exercise Psychology 1997;19:249-277.

2 Chang YK, Labban JD, Gapin JI, Etnier JL: The effects of acute exercise on cognitive performance: A meta-analysis. Brain Research 2012;1453:87-101.

3 Smith PJ, Blumenthal JA, Hoffman BM, Cooper H, Strauman TA, Welsh-Bohmer K, Browndyke JN, Sherwood A: Aerobic exercise and neurocognitive performance: A meta-analytic review of randomized controlled trials. Psychosomatic Medicine 2010;72:239-252.

4 Black JE, Isaacs KR, Anderson BJ, Alcantara AA, Greenough WT: Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. Proceedings of the National Academy of Sciences of the United States of America 1990;87:5568-5572.

5 Neeper SA, Gomez-Pinilla F, Choi J, Cotman C: Exercise and brain neurotrophins [2]. Nature 1995;373:109.

6 Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, Chason J, Vakil E, Bardell L, Boileau RA, Colcombe A: Ageing, fitness and neurocognitive function [7]. Nature 1999;400:418-419.

7 Lustig C, Shah P, Seidler R, Reuter-Lorenz PA: Aging, training, and the brain: A review and future directions. Neuropsychology Review 2009;19:504-522.

8 Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, Kim JS, Heo S, Alves H, White SM, Wojcicki TR, Mailey E, Vieira VJ, Martin SA, Pence BD, Woods JA, McAuley E, Kramer AF: Exercise training increases size of hippocampus and improves memory. Proceedings of the National Academy of Sciences of the United States of America 2011;108:3017-3022.

9 Seifert T, Brassard P, Wissenberg M, Rasmussen P, Nordby P, Stallknecht B, Adser H, Jakobsen AH, Pilegaard H, Nielsen HB, Secher NH: Endurance training enhances bdnf release from the human brain. American Journal of Physiology - Regulatory Integrative and Comparative Physiology 2010;298:R372-R377.

10 Um HS, Kang EB, Koo JH, Kim HT, Jin L, Kim EJ, Yang CH, An GY, Cho IH, Cho JY: Treadmill exercise represses neuronal cell death in an aged transgenic mouse model of alzheimer's disease. Neuroscience Research 2011;69:161-173.

11 Zoladz JA, Pilc A: The effect of physical activity on the brain derived neurotrophic factor: From animal to human studies. Journal of Physiology and Pharmacology 2010;61:533-541.

12 Gunstad J, Benitez A, Smith J, Glickman E, Spitznagel MB, Alexander T, Juvancic-Heltzel J, Murray L: Serum brain-derived neurotrophic factor is associated with cognitive function in healthy older adults. Journal of Geriatric Psychiatry and Neurology 2008;21:166-170.

13 Gomez-Pinilla F, Vaynman S, Ying Z: Brain-derived neurotrophic factor functions as a metabotrophin to mediate the effects of exercise on cognition. European Journal of Neuroscience 2008;28:2278-2287.

14 Zhu XH, Yan HC, Zhang J, Qu HD, Qiu XS, Chen L, Li SJ, Cao X, Bean JC, Chen LH, Qin XH, Liu JH, Bai XC, Mei L, Gao TM: Intermittent hypoxia promotes hippocampal neurogenesis and produces antidepressant-like effects in adult rats. Journal of Neuroscience 2010;30:12653-12663.

15 Xie H, Leung KL, Chen L, Chan YS, Ng PC, Fok TF, Wing YK, Ke Y, Li AM, Yung WH: Brain-derived neurotrophic factor rescues and prevents chronic intermittent hypoxia-induced impairment of hippocampal long-term synaptic plasticity. Neurobiology of Disease 2010;40:155-162.

16 Acree LS, Longfors J, Fjeldstad AS, Fjeldstad C, Schank B, Nickel KJ, Montgomery PS, Gardner AW: Physical activity is related to quality of life in older adults. Health and Quality of Life Outcomes 2006;4

17 Reid KJ, Baron KG, Lu B, Naylor E, Wolfe L, Zee PC: Aerobic exercise improves self-reported sleep and quality of life in older adults with insomnia. Sleep Medicine 2010;11:934-940.

18 Stewart KJ, Turner KL, Bacher AC, DeRegis JR, Sung J, Tayback M, Ouyang P: Are fitness, activity, and fatness associated with health-related quality of life and mood in older persons? Journal of Cardiopulmonary Rehabilitation 2003;23:115-121.
19 Folstein MF, Folstein SE, McHugh PR: 'Mini mental state'. A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research 1975;12:189-198.
20 Brickenkamp R: Test: Testmaterial. Verlag für Psychologie Hogrefe, 1981.
21 Oswald WD, Roth E: Der zahlen-verbindungs-test(zvt): Handanweisung. Verlag für Psychologie C. J. Hogrefe, 1978.
22 Brähler E, Brickenkamp R: Brickenkamp-handbuch psychologischer und pädagogischer tests. Hogrefe, Verlag für Psychologie, 2002.
23 Brickenkamp R, Zillmer E: The d2 test of attention. Hogrefe & Huber, 1998.
24 Oswald WD: Psychometric tests and razing scales for gerontopsychological problems. PSYCHOMETRISCHE VERFAHREN UND FRAGEBOGEN FUR GERONTOPSYCHOLOGISCHE UNTERSUCHUNGEN 1979;12:341-350.
25 Jenkinson C, Peto V, Coulter A: Measuring change over time: A comparison of results from a global single item of health status and the multi-dimensional sf-36 health status survey questionnaire in patients presenting with menorrhagia. Quality of Life Research 1994;3:317-321.
26 Buysse DJ, Reynolds Iii CF, Monk TH, Berman SR, Kupfer DJ: The pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiatry Research 1989;28:193-213.
27 Beaudreau SA, Spira AP, Stewart A, Kezirian EJ, Lui LY, Ensrud K, Redline S, Ancoli-Israel S, Stone KL: Validation of the pittsburgh sleep quality index and the epworth sleepiness scale in older black and white women. Sleep Medicine 2012;13:36-42.
28 Cohen J: A power primer. Psychological Bulletin 1992;112:155-159.
29 Kleim JA, Cooper NR, VandenBerg PM: Exercise induces angiogenesis but does not alter movement representations within rat motor cortex. Brain Research 2002;934:1-6.
30 Gozal D, Kheirandish-Gozal L: Cardiovascular morbidity in obstructive sleep apnea: Oxidative stress, inflammation, and much more. American Journal of Respiratory and Critical Care Medicine 2008;177:369-375.
31 Row BW, Kheirandish L, Neville JJ, Gozal D: Impaired spatial learning and hyperactivity in developing rats exposed to intermittent hypoxia. Pediatric Research 2002;52:449-453.
32 Burtscher M, Mairer K, Wille M, Gatterer H, Ruedl G, Faulhaber M, Sumann G: Short-term exposure to hypoxia for work and leisure activities in health and disease: Which level of hypoxia is safe? Sleep and Breathing 2012;16:435-442.
33 Rybnikova E, Vataeva L, Tyulkova E, Gluschenko T, Otellin V, Pelto-Huikko M, Samoilov MO: Mild hypoxia preconditioning prevents impairment of passive avoidance learning and suppression of brain ngfi-a expression induced by severe hypoxia. Behavioural Brain Research 2005;160:107-114.
34 Colcombe S, Kramer AF: Fitness effects on the cognitive function of older adults: A meta-analytic study. Psychological Science 2003;14:125-130.
35 Lu L, Dempsey J, Liu SY, Bossert JM, Shaham Y: A single infusion of brain-derived neurotrophic factor into the ventral tegmental area induces long-lasting potentiation of cocaine seeking after withdrawal. Journal of Neuroscience 2004;24:1604-1611.
36 Poo MM: Neurotrophins as synaptic modulators. Nature Reviews Neuroscience 2001;2:24-32.
37 Rose CR, Blum R, Kafitz KW, Kovalchuk Y, Konnerth A: From modulator to mediator: Rapid effects of bdnf on ion channels. BioEssays 2004;26:1185-1194.
38 Miller DI, Taler V, Davidson PSR, Messier C: Measuring the impact of exercise on cognitive aging: Methodological issues. Neurobiology of Aging 2012;33:622.e629-622.e643.
39 Silveira E, Taft C, Sundh V, Waern M, Palsson S, Steen B: Performance of the sf-36 health survey in screening for depressive and anxiety disorders in an elderly female swedish population. Quality of Life Research 2005;14:1263-1274.