CNS & Neurological Disorders - Drug Targets, 2017, *16*, 638-651

REVIEW ARTICLE

Exercise Induced Neuroplasticity to Enhance Therapeutic Outcomes of Cognitive Remediation in Schizophrenia: Analyzing the Role of Brain-derived Neurotrophic Factor

Carlos Campos[1,2,*], Nuno B.F. Rocha[1], Eduardo Lattari[2,3], António E. Nardi[2] and Sérgio Machado[2,3]

[1]*Polytechnic Institute of Porto, Health School, Porto, Portugal;* [2]*Laboratory of Panic & Respiration (LABPR), Institute of Psychiatry (IPUB), Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil;* [3]*Physical Activity Neuroscience Laboratory, Physical Activity Sciences Postgraduate Program - Salgado de Oliveira University (UNIVERSO), Niterói, Brazil*

ARTICLE HISTORY

Received: December 16, 2015
Revised: December 05, 2016
Accepted: December 09, 2016

DOI:
10.2174/1871527315666161223142918

Abstract: ***Background***: Cognitive impairment is a major manifestation of schizophrenia and a crucial treatment target as these deficits are closely related to patients' functional outcomes. Cognitive remediation is the gold-standard practice to address cognitive deficits in schizophrenia. There is clear evidence stating that cognitive remediation improves cognitive function and promotes structural neuroplastic changes in patients with schizophrenia, with brain-derived neurotrophic factor (BDNF) expression emerging as a potential biomarker for its efficacy. This is particularly important as there is clear evidence relating atypical BDNF expression to cognitive impairment in patients with schizophrenia. Despite the valuable role of cognitive remediation in the management of schizophrenia, there is still a need to develop methods that allow maximizing its efficacy.

Method and Results: In this review, we present a hypothesis arguing that cognitive remediation efficacy for patients with schizophrenia can be enhanced by aerobic exercise-induced BDNF upregulation. There have been a few trials reporting that combining aerobic exercise with cognitive training was superior to cognitive training alone to improve cognitive functioning in patients with schizophrenia. Furthermore, there is preliminary evidence suggesting that combined aerobic and cognitive training can increase peripheral BDNF levels.

Conclusion: Thereby, engaging in aerobic exercise in close temporal proximity to cognitive remediation may allow achieving a state of neuroplastic readiness in the brain, facilitating cognitive functioning enhancement. Although this hypothesis still lacks evidence, future clinical trials using cognitive remediation for schizophrenia should explore strategies to maximize neuroplasticity and achieve optimal cognitive improvements.

Keywords: Brain-derived neurotrophic factor, Cognitive remediation, Exercise, Learning, Neuroplasticity, Schizophrenia.

1. INTRODUCTION

Cognitive impairment is a major manifestation of schizophrenia and a crucial treatment target as these deficits are closely related to patients' functional and vocational outcomes [1-5]. Although cognitive functioning is widely heterogeneous in this population [2, 6], cognitive impairment is observed in the majority of patients, even prior to disease onset [7, 8]. Patients with schizophrenia experience global cognitive dysfunction but deficits are mainly observed in working memory, executive function, attention, verbal and visual memory/learning and processing speed [9] as well as in social cognitive skills such as theory of mind and emotion perception [10].

Pharmacological interventions have been fairly modest addressing cognitive impairments [11, 12]. Therefore, alternative interventions such as cognitive remediation have been presented as promising tools to target cognitive functioning [13]. Cognitive remediation has been defined by the Cognitive Remediation Experts Workshop has an intervention targeting cognitive deficits (*e.g.* attention, memory, executive function, social cognition) using the scientific principles of learning with the ultimate goal of improving functional outcomes [14]. However, although the final goal of cognitive remediation is functional improvement, it also aims to reduce the cognitive deficits detected by standardized tests [15]. Several meta-analyses have described significant effects of

*Address correspondence to this author at the Health School, Polytechnic Institute of Porto, Porto, Portugal, Rua Dr. António Bernardino de Almeida, 400 Box: 4200-072, Porto, Portugal; Tel: +315222061000;
E-mail: carlosm.campos77@gmail.com

1996-3181/17 $58.00+.00

cognitive remediation on cognitive performance of patients with schizophrenia [16-18]. A recent meta-analysis found small to moderate effects of cognitive remediation on cognitive outcomes immediately after the intervention and on the follow-up assessments of patients with schizophrenia [19]. Furthermore, there has been evidence supporting the effects of cognitive remediation on social cognition, with significant positive effects reported regarding theory of mind and emotion perception deficits [20, 21].

The underlying theoretical framework for cognitive remediation is the cognitive neuroscience basis of learning, which assumes that at any point throughout the lifespan, brain capacity can be restored through neuroplasticity and neurogenesis [15, 22, 23]. Thereby, cognitive remediation provides a proper stimulating environment to harness the brain's plastic ability, inducing neural changes that may allow to improve cognitive functioning. Currently, there have been several molecular, functional and structural neuroimaging studies reporting brain changes following cognitive remediation, providing evidence for its biological validity [13, 24, 25]. Thereby, cognitive remediation seems to activate neuroplastic and brain repair mechanisms, although researchers have not been able to pinpoint the underlying neurobiological processes.

Brain-derived neurotrophic factor (BDNF) is a well-known neurotrophin that has been proposed as a possible biomarker for cognitive enhancement in schizophrenia [26, 27]. BDNF has been linked to neurodevelopment and neuroprotection of the central nervous system, playing a critical role in synapse regulation, learning, and memory [28, 29]. Its role on neuroplastic processes is associated with axonal and dendritic growth and remodeling, neuronal differentiation, synaptic transmission and growth [30, 31]. The neural dysfunction observed in psychiatric disorders such as schizophrenia has been related to impaired cortical circuitry and synaptic transmission, which could be caused by changes in neurotrophins synthesis and/or expression. [32]. This hypothesis is closely related to the contribution of BDNF to cognitive enhancement. Furthermore, there is also clear evidence stating that exercise can improve cognitive function [33-36] and increase blood BDNF levels both in healthy subjects and clinical populations [37], which lead several researchers to explore the effects of combining cognitive remediation with exercise for several populations [38-41].

Thereby, how can cognitive remediation and exercise be combined to maximize their effects on cognitive performance of schizophrenia patients? And can BDNF play a critical role in enhancing the effects of cognitive remediation? This report aims to present evidence that supports the following hypothesis: aerobic exercise preceding cognitive remediation can increase its effectiveness in patients with schizophrenia by inducing a neuroplastic readiness state through BDNF levels increase.

2. NEURAL CORRELATES OF COGNITIVE REMEDIATION IN SCHIZOPHRENIA

Brain changes following cognitive remediation in patients with schizophrenia have been widely supported in the last decade. There are several systematic reviews addressing the neural and biological correlates of cognitive improvements following cognitive remediation in these patients [13, 24, 25]. Recently, Wei *et al.* [42] performed an activation likelihood estimation meta-analysis of functional magnetic resonance imaging (fMRI) and positron emission tomography studies and found that cognitive remediation might improve cognition in patients with schizophrenia by significantly enhancing brain activation in several regions from the frontal and parietal cortex. Another systematic review of studies targeting social cognitive deficits suggests that cognitive remediation is associated with a wide range of functional and structural changes in the social brain, namely prefrontal regions, the limbic system and perceptual areas [43].

The mostly explored method to study the neuroplastic effects of cognitive remediation in schizophrenia has been fMRI, with most studies highlighting its effects on the prefrontal cortex (PFC); [44-49]. Further evidence supporting the role of the PFC in cognitive remediation has been provided by Pu *et al.* [50] using near-infrared spectroscopy, founding increased activity in bilateral dorsolateral PFC, ventrolateral PFC and right frontopolar PFC after a computer-based cognitive remediation intervention. Additionally, there was also evidence of increased activity after cognitive remediation in several brain regions crucial to cognitive function such as the occipital lobe, inferior and superior parietal cortex, cingulate cortex, among other [44, 45, 51]. Studies exploring brain activity changes following cognitive remediation interventions that target social cognitive deficits have also found interesting findings. For instance, Hooker *et al.* [52, 53] found increased neural activity after training in the bilateral amygdala, right putamen, right medial prefrontal cortex and postcentral gyrus, with improvements predicting performance on emotion processing measures.

Beyond the evidence of fMRI studies, there are also several reports from electrophysiological studies (electroencephalography and event-related potentials) that report normalization of early perceptual processes and cognitive functioning [54-56]. There are also reports of increased efficiency in facial emotion processing after cognitive remediation targeting social cognition [57, 58].

Finally, there are also a few studies reporting morphological changes after cognitive remediation. Eack *et al.* [59] designed a 2-year cognitive remediation trial that was able to achieve structural changes in the brain of patients with schizophrenia, allowing a significant gray matter volume increase in the left amygdala and inhibiting the progressive loss of gray matter in the left parahippocampal and fusiform gyrus in comparison to the control condition. Moreover, these effects on gray matter volume were remarkably associated with improved social cognitive functioning. A study using diffusion tensor imaging also found increased fractional anisotropy after cognitive remediation in the body and genu of the corpus callosum and right posterior thalamic radiations, whereas the active control group exhibited decreased fractional anisotropy in the bilateral superior longitudinal fasciculus and left inferior longitudinal fasciculus [60].

Summing it up, there is evidence from both functional and structural imaging procedures as well as from electrophysiological studies supporting the role of cognitive remediation in the neuroprotection and prevention of progressive neurodegeneration in schizophrenia. More importantly, the

reported neural correlates of cognitive remediation are clearly related to cognitive improvements after the intervention. However, it is important to understand the neurobiological pathways that may underlie these changes and support cognitive function in patients with schizophrenia, allowing researchers and clinicians to develop intervention protocols that maximize treatment effects for this population.

3. BDNF AS A BIOMARKER FOR COGNITIVE REMEDIATION EFFECTIVENESS

In the last few years, BDNF has emerged as a potential candidate to explain the neuroplastic changes observed following cognitive remediation. There are several reviews exploring the role of BDNF in the cellular and molecular mechanisms which underlie cognitive functioning, especially learning and memory [28, 61, 62]. BDNF secretion is required for long-term potentiation and long-term depression as well as for cellular plasticity mechanisms that underlie learning and memory. Furthermore, BDNF overexpression can increase the number of dendritic spines or enhance dendritic complexity in specific brain tissues, making it an important contributor to hippocampal-dependent learning [63, 64].

Several animal studies explored the effects of genetically or virally induced BDNF ablation on mice, reporting impairments in various cognitive functions, mainly hippocampal-dependent tasks such as context-dependent memory [65], spatial learning and novel object recognition [66, 67], but also in PFC-related functions such as spatial memory reversal and contextual memory extinction [68]. In contrast, transgenic overexpression of BDNF in the hippocampus and cerebral cortex enhanced learning and memory in a water maze task [69]. Furthermore, striatal BDNF infusions improved cognitive flexibility (discrimination learning and strategy shifting) in rats [70].

BDNF gene expression also seems to play a critical role in human cognitive functioning and its underlying brain regions, namely the hippocampus and prefrontal regions [71]. The functional BDNFval66met polymorphism has been associated with abnormal intracellular trafficking and activity-dependent secretion of BDNF, leading to impaired memory and hippocampal dysfunction [72]. Furthermore, Hariri *et al.* [73] reported that the interaction between this genotype and hippocampal response during encoding significantly accounted for recognition memory performance. Evidence from both healthy and clinical populations also suggests that functional BDNF polymorphisms can be associated with changes in executive functioning [74-76].

As evidence regarding the role of BNDF on learning and memory consolidated, researchers postulated that this protein could mediate the cognitive improvements achieved by cognitive remediation. Animal studies using enriched environments that simulate cognitive stimulation have explored whether this intervention can modulate BDNF in the brain. Exposing animals to enriched environments has been associated with BDNF enhancement in several brain regions including the cerebral cortex, basal forebrain, and hindbrain [77] as well as the cerebellum [78]. However, the most consistent increases have been reported in the hippocampus [77, 79-81]. Falkenberg *et al.* [82] actually reported a correlation between improved spatial memory and increased BDNF mRNA in rats' hippocampus after exposing them to an enriched environment. There is also recent evidence suggesting that BDNF plays an intrinsic role in enhanced plasticity and memory following enriched environment exposure [79] as well as in experience-dependent plasticity related to auditory stimuli [83].

More recently, there has been evidence from human studies with several clinical populations suggesting that BDNF may be one of the neurobiological correlates of cognitive remediation (Table **1**). Angelucci *et al.* [27] applied a 12-session executive functioning training program to patients with Parkinson's disease with mild cognitive impairment and found significant increases in serum BDNF levels after the intervention in comparison to the placebo group, although there were no significant correlations between BDNF increase and cognitive improvement. A recent study from Casoli *et al.* [84] with subjects with mild cognitive impairment investigated the changes in BDNF mRNA level of peripheral lymphocytes after a 10-session cognitive training protocol. Interestingly, the cognitive training group experienced a decrease in BDNF mRNA. The authors argued that a compensatory mechanism may increase BDNF levels in mild cognitive impairment and cognitive training may allow to restore pre-morbid levels. Finally, Pressler *et al.* [85] designed a trial with patients with heart failure using a computerized cognitive training program that targeted auditory information encoding, recall, and manipulation. After 8-weeks of intervention with 5 sessions per week, participants assigned to the training program presented improved working memory and decreased decline in processing speed. Moreover, serum BDNF levels significantly increase in the experimental group in comparison to the control group.

There are also a few reports addressing the relationship between BDNF and cognitive remediation in patients with schizophrenia. Vinogradov *et al.* [26] and Adcock *et al.* [54] applied a 10-week computer-based auditory training program to 56 patients with chronic schizophrenia and found improvements in verbal working memory, immediate verbal learning, and verbal memory. More importantly, there was a significant increase in BDNF levels in comparison to the control group. There was no significant relationship between increased BDNF and improved cognitive scores, although a significant positive association with enhanced quality of life was reported. A subsequent report from the same team with an enlarged sample still provided evidence of cognitive improvement and BDNF increase after the intervention. Effect size analysis actually showed moderate training effects on BDNF levels since week 2 that remained around the same magnitude until the end of the intervention [86].

Another cognitive remediation trial explored whether functional BDNF val66met polymorphism predicted treatment response to a 16-session computerized cognitive remediation program for paranoid schizophrenia [87]. There was no significant evidence supporting the role of the polymorphism as a prognostic factor for cognitive remediation but quite interestingly the participants with the BDNF val66met genotype were assigned to exercises with a lower degree of difficulty by the cognitive training software in the beginning of the intervention.

Table 1. Studies assessing BDNF changes after cognitive remediation.

Study Authors	Participants	Cognitive Remediation	Control Group	Intervention Length Frequency Session Duration	BDNF Outcome	Major Findings
Adcock *et al.* (2009) Vinogradov *et al.* (2009)	Chronic schizophrenia outpatients (n=56) CR (n=30) CG (n=26)	Computerized auditory training (auditory processing and working memory)	Computer games	10 weeks 5 sessions/week 1 hour/session	Serum BDNF	↑ Serum BDNF levels 2 and 10 weeks after CR in comparison to CG. Association between BDNF increase and quality of life improvements
Casoli *et al.* (2009)	Mild cognitive impairment elderly (n=19) CR (n=14) CG (n=5)	Pen & pencil cognitive training targeting temporal-spatial orientation and memory	Education	10 sessions 1 session/week 1 hour/session	BDNF mRNA in peripheral lymphocytes	↓ BDNF mRNA levels in the CR but not in the CG after the intervention.
Mak *et al.* (2013)	Paranoid schizophrenia outpatients (n=81 in total) CR (n=41) CG (n=40)	Computerized cognitive training (multimodal)	Treatment as usual	16 sessions 2 sessions/week 40 min/session	BDNF Genotyping	Genotypes did not predict cognitive improvement; Polymorphism val/met was associated with lower scores (easier exercises) during training.
Pressler *et al.* (2015)	Heart failure patients (n=27) CR (n=) CG (n=)	Computerized cognitive training (auditory training)	Health education	8 weeks 5 sessions/week 1 hour/session	Serum BDNF BDNF Genotyping	↑ Serum BDNF levels in CR after training and ↓ Serum BDNF levels in CG after the intervention regardless of BDNF val/met polymorphism
Angelucci *et al.* (2015)	Parkinson's disease outpatients (n=15) CR (n=7) CG (n=8)	Pen & pencil cognitive training of shifting abilities	Simple cognitive training (sustained attention, language abilities) plus respiratory exercises	1-month 3 sessions/week 45 min/session	Serum BDNF	↑ BDNF serum levels in the CR but not in the CG after the intervention
Fisher *et al.* (2016)	Chronic schizophrenia outpatients (n=87) CR (n=46) CG (n=41)	Computerized auditory training	Computer games	Computerized auditory training	Serum BDNF	↑ Serum BDNF levels 2 and 10 weeks after CR in comparison to CG. No association between BDNF increase and cognitive improvement.

CR: cognitive remediation group; CG: control group.

The relationship between BDNF, cognition, and learning is quite well established in both animals and humans. Moreover, although evidence it not very robust, preliminary findings from human studies seem to support the hypothesis that BDNF is a biomarker of cognitive remediation efficacy.

4. BDNF AND COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

As evidence supporting the role of BDNF in cognitive enhancement increases, it becomes important to understand how this neurotrophin engages in the brain of patients with schizophrenia and its role on cognitive impairment. However, it is important to highlight that understating the association between BDNF and schizophrenia is quite hard as there are several potential confounders such as medication side-effects, phenotype, symptom severity and duration [88].

Evidence regarding the role of BDNF in schizophrenia psychopathology comes from several fields of study. Genetic studies have associated functional BDNF polymorphisms (Val66Met and C-207T9) to increased susceptibility to schizophrenia [89]. A meta-analysis developed by Jönsson *et al.* [90] with Caucasian individuals from the US and several European countries actually found an association between both functional polymorphisms and the presence of schizophrenia. However, other meta-analyses have reported that this association cannot be found in Asian populations [91, 92].

Other studies actually explore the association between BDNF polymorphisms and cognitive deficits of patients with schizophrenia. Val66Met polymorphism has been associated with deficits in executive function and memory [93, 94], impaired visuospatial/constructional performance and attentional decrements in male patients with schizophrenia [95]. Rybakowski *et al.* [96] did not found a relationship between Val66Met polymorphism and executive functioning, although patients with Val/Val genotype had a superior working memory performance. Further evidence of disease-specific Val66Met polymorphism involvement in schizophrenia brain dysfunction has been supplied by a positron emission tomography study that reported significantly less hippocampal regional cerebral blood flow in patients harboring a Metallele, while there were no significant associations in healthy controls [97].

Although way scarce when compared to evidence from genetic studies, the role of BDNF in schizophrenia has also been supported by postmortem studies. Durany *et al.* [98] found increased BNDF concentrations in several cortical regions and a decrease in hippocampal tissues, although other authors actually found increased levels in the hippocampus [99]. However, there have been several studies describing reduced BDNF levels in prefrontal regions of patients with schizophrenia [100-102].

The most commonly used approach to study the role of BDNF in schizophrenia has been the measurement of plasma/serum levels, allowing to understand if BNDF concentration fluctuates across the clinical evolution of the disease [93]. A meta-analysis by Green *et al.* [103] concluded that blood levels of BDNF are reduced in medicated and drug-naive patients with schizophrenia. More recently, a new meta-analysis also found that peripheral BDNF levels were moderately reduced in schizophrenia in comparison to control subjects, with concentration decreasing as disease duration increased [104]. However, it is important to highlight that there is a significant heterogeneity across study results as several authors did not found any differences in peripheral BDNF levels [105-107] and some even found higher levels in patients [108].

More importantly, there have been efforts to understand the association between BDNF levels and cognitive performance in schizophrenia. BDNF serum levels have been positively associated with immediate memory [95] and other cognitive tests [109]. Carlino *et al.* [110] found that reduced serum truncated-BDNF/total BDNF ratio correlated with poorer performance on processing speed, attention, executive function, and working memory. Moreover, it seems that decreased BDNF serum levels and cognitive impairment in schizophrenia are dependent on the BDNFVal66Met polymorphism [95]. More recently, Zhang *et al.* [111] described an association between BDNF levels, immediate memory, and global cognitive functioning only in female patients, suggesting a possible mechanism underlying gender-related differences in cognitive impairment in schizophrenia.

There is also evidence describing the positive association between plasma BDNF and several cognitive domains in first-episode psychosis patients, including learning ability, immediate and delayed memory, abstract thinking and processing speed, even after controlling for medication, IQ, drug use and negative symptoms [112]. BDNF seems to play a role in the course and onset of schizophrenia as there is an association between low serum BDNF levels and reduced hippocampal volume in first-episode drug-naive patients [113].

Although researchers are far from understanding the mechanisms that underlie BDNF changes in schizophrenia, it is safe to state that this neurotrophin is implicated in the pathophysiology of schizophrenia. Furthermore, BDNF seems an important candidate to help us understand the molecular and cellular mechanisms that underlie cognitive impairment in individuals with schizophrenia [93].

5. EXERCISE-INDUCED COGNITIVE AND BDNF ENHANCEMENT IN SCHIZHOPHRENIA

BDNF may be a critical biological footprint of cognitive impairment in schizophrenia, which led researchers to explore interventions that could modulate its expression in the brain. Although cognitive remediation is a highly effective tool for cognitive enhancement and has been associated with BDNF levels increase, exercise has also shown promising results to improve cognitive performance and brain function in patients with schizophrenia (Table **2**), [114-116]. Zwick *et al.* [117] reported that exercise was effective to improve working memory, short-term memory and verbal learning in patients with paranoid schizophrenia. Falkai *et al.* [118] applied a cycling aerobic exercise protocol for 3 months and found enhanced short-term memory in comparison to an active control intervention. More recently, a pre-experimental study using high-velocity resistance circuit for chronic patients also found significant intervention effects on processing speed and working memory [119].

It seems that exercise enhances memory and learning in patients with schizophrenia, but it is also important to highlight that a few trials have also explored the neural correlates that support these improvements. The first major findings regarding exercise-induced neuroplastic changes in schizophrenia were reported by Pajonk *et al.* [120], who found increased hippocampal volume after 3 months of aerobic exercise in chronic patients. Interestingly, subsequent analysis explored whether aerobic exercise also induced neocortical changes but found no significant effects in gray matter density and cortical expansion across the whole cortex [118]. This may suggest specific exercise effects on the hippocampus, although other authors have found no changes in hippocampal volume after a 6-month multimodal aerobic exercise program [121]. A recent study using diffusion tension imaging found very significant treatment effects after a 6-month bicycle ergometer aerobic exercise protocol, improving the integrity of white matter fiber tracts, while participants in the active control group experienced decreased fiber integrity [122]. These findings were mainly prominent in motor functioning related tracts (corticospinal tract and superior longitudinal fascicle) but findings on the inferior longitudinal fascicle, inferior fronto-occipital fascicle, and anterior thalamic radiation may also suggest improved efficiency in cognitive functions such as attention, visual and verbal processing, executive function and memory encoding.

The potential of exercise for cognitive improvement in patients with schizophrenia is quite clear and researchers are getting increasingly closer to the neural correlates that support these changes. But could it be that exercise shares the same neurobiological mechanisms that support cognitive enhancement in cognitive remediation? Can neurotrophic factors such as BDNF be mediators of exercise-induced cognitive effects?

Although several mechanisms have been proposed to debate exercise-induced cognitive improvement, in the last decade researchers developed numerous studies to understand the relationship between BDNF, exercise, and cognitive functioning. Neeper *et al.* [123] were the first to report that physical activity could increase BDNF levels in the rat's brains by upregulating its expression the hippocampus and caudal neocortex. Further evidence from animal studies suggests that the potential benefits of exercise on cognitive function are inhibited when BDNF action in the hippocampus is blocked [124].

Table 2. Exercise-induced cognitive and neuroplastic changes in schizophrenia.

Study Authors	Participants	Exercise Modality	Intervention Length Frequency Session Duration	Intensity	Control Groups	Major Findings
Pajonk *et al.* (2010)	Chronic SZ outpatients (n=16) EG (n=13) CG (n=11)	Aerobic exercise (cycling)	3-months 3 sessions/week 30 min/session	*Heart rate* ±10 beats/min *Blood lactate* 14-18 mg/dL	Playing table football	↑ Hippocampal volume in the EG (12%) in comparison to the CG (−1%); Correlation between hippocampal volume changes and improvements VO2max/kg and maximum power per kilogram (r=0.72; r=0.83).
Zwick *et al.* (2010)	Paranoid SZ inpatients (n=37) EG (n=20) CG (n=17)	No info	4 sessions/week 30 min/session	No info	Occupational Therapy	↑ Working memory, short term memory and verbal learning in the EG in comparison to the CG
Falkai *et al.* (2012)	Chronic SZ outpatients (n=16) EG (n=8) CG (n=8)	Aerobic exercise (cycling)	3-months 3 sessions/week 30 min/session	*Heart rate* ±10 beats/min *Blood lactate* 14-18 mg/dL	Playing table football	↑ Short-term memory in the EG after exercise; No significant changes in gray matter density and cortical expansion.
Takahashi *et al.* (2012)	Chronic SZ outpatients (n=23) EG (n=13) CG (n=10)	Aerobic exercise (multimodal) plus nutrition and medication counseling	3-months 12 sessions/week 30-60 min/session	RPE 11-13	Treatment as usual	↑ Activation in the extrastriate body area f the posterior temporal-occipital cortex was observed in the EG after exercise.
Scheewe *et al.* (2013)	Chronic SZ outpatients (n=63) EG (n=31) CG (n=32)	Aerobic exercise (multimodal) and strength exercises	6-months 2 sessions/week 40 min aerobic exercise plus 20 min strength exercises/session	Gradual increase between 45-75% HRR	Occupational therapy	Association between cardiorespiratory fitness (peak work rate at exhaustion) improvement and cerebral matter volume increase as well as lateral and third ventricle volume decrease.
Kim *et al.* (2014)	Chronic SZ outpatients (n=36) EG (n=24) CG (n=12)	Combined exercise (aerobic exercise plus strength training)	3-month 3 sessions/week 25 min aerobic exercise plus 25 min strength training/session	*Strength Training* RPE 12-13 *Aerobic exercise* Gradual increase between 50-70% HRR	Stretching, dancing, and recreation activities (1h/week)	↑ Serum BDNF values only in the EG.
Kimhy *et al.* (2015) Kimhy *et al.* (2016)	Chronic SZ outpatients (n=33) EG (n=16) CG (n=17)	Aerobic exercise (multimodal)	3-months Aerobic exercise 3 sessions/week 1 hour/session	Gradual increase between 60-75% HRmax	Standard psychiatric treatment	↑ Overall neurocognitive functioning in the EG (15.1%) in comparison to the CG (-2.0%); ↑ Serum BDNF levels in the EG (11.1%) in comparison to the CG (1.9%); BDNF changes contributed 14.6% to neurocognitive improvement after training.
Strassnig *et al.* (2015)	Chronic SZ outpatients (n=9) Bipolar disorder outpatients (n=3)	High-velocity endurance training circuit	2-months 2 sessions/week	Increase loading across training based on max power production	None	↑ Global cognitive functioning, speed of processing and working memory after training.
Svatkova *et al.* (2015)	Chronic schizophrenia outpatients (n=33) EG (n=16) CG (n=17)	Aerobic exercise (multimodal) and strength exercises	6-months 2 sessions/week 40 min aerobic exercise plus 20 min strength exercises/session	No info	Occupational therapy	↑ Fractional anisotropy in the left corticospinal tract, left superior longitudinal fascicle and forceps major of corpus callosum in the EG in comparison to the CG.

SZ: schizophrenia; EG: exercise group; CG: control group; VO2max/kg: maximum oxygen consumption per kilogram; RPE: rating of perceived exertion; HRR: heart rate reserve; HRmax: maximal heart rate.

In human studies, evidence regarding enhanced BDNF levels after aerobic exercise has been pretty well-established by several systematic reviews [37, 125, 126]. A recent meta-analysis explored the effects of exercise on BDNF expression across healthy subjects and clinical populations, with findings proving reliable evidence that both acute and regular exercise can increase peripheral BDNF levels [37]. More precisely, moderate effects were found on BDNF levels after a single session of acute exercise. Chronic regular exercise was associated with small effects in resting BDNF levels and a moderate effect in single bout exercise-induced BDNF increase after the completion of training programs.

It is important to highlight that there are several studies with neuropsychiatric disorders reporting exercise-induced BDNF increase, including depression [127-129], panic disorder [130], mild cognitive impairment [131] and Alzheimer's disease [132]. Kim *et al.* [133] were the first to report the effects of exercise on peripheral BDNF levels in a sample of 86 patients with schizophrenia. After a 3-month protocol of combined strength and aerobic exercise, serum BDNF levels significantly increased in comparison to the control group. More recently, Kimhy *et al.* [134] designed a randomized clinical trial to assess the effects of a 3-month aerobic exercise protocol for chronic patients in serum BDNF levels. Besides significant improvements in global cognitive functioning, the authors also reported a higher increase in BDNF levels in the experimental group (11%) in comparison to the control group (1.9%). However, the major finding was the result of a hierarchical step-wise regression analysis that found that after controlling for a series of variables (*e.g*. age, gender, medication), changes in BDNF levels significantly accounted for 14.6% of the variance in cognitive functioning.

Looking at all the pieces together, it is possible to understand that exercise is a valuable tool for cognitive enhancement in patients with schizophrenia and that there is preliminary evidence linking aerobic exercise, BDNF upregulation and cognitive improvement.

6. PROMOTING COGNITIVE REMEDIATION THROUGHT EXERCISE-INDUCED PLASTICITY

Looking at the previously described evidence there are several assumptions to highlight regarding cognitive remediation and BDNF expression in schizophrenia:

i). Cognitive remediation effectively improves cognitive function and promotes functional and structural neuroplastic changes in patients with schizophrenia;

ii). Evidence from genetic, post-mortem and neurobiological studies noticeably indicate that BDNF expression is atypical in patients with schizophrenia, with clear evidence of reduced peripheral BDNF levels;

iii). There is evidence suggesting that BDNF expression may be a biomarker of cognitive remediation in several clinical populations, including schizophrenia.

Despite the valuable role of cognitive remediation in the management of schizophrenia, its effects are frequently modest and alternative methods to enhance its efficacy should be studied. Exercise has been growingly explored in schizophrenia as it seems to enhance cognitive performance, neural functioning, and neuroplastic processes through BDNF levels increase. Thereby, there is evidence suggesting that BDNF may be a biomarker for cognitive enhancement in both aerobic exercise and cognitive remediation.

Our hypothesis argues that cognitive remediation efficacy can be enhanced by aerobic exercise induced BDNF upregulation (Fig. **1**). To sustain this hypothesis, it's important to notice evidence from trials combining exercise plus cognitive training. A recent systematic review found that simultaneous or subsequently combined exercise and cognitive remediation seems to be more effective to improve cognitive functioning that either intervention alone [135]. There have been several trials reporting that combined cognitive training and exercise is superior to either intervention alone to improve cognitive functioning in elderly participants, namely divided attention [136, 137], shifting attention and working memory [138], verbal memory [139], overall memory quotient [140], global cognitive performance and independent living measures [141].

More recently, there have been a few trials exploring the combination of cognitive remediation and aerobic exercise in patients with schizophrenia. Oertel-Knochel *et al.* [142] compared 12 sessions of cognitive training combined with either aerobic exercise or relaxation training. The protocol lasted 4 weeks (3 sessions per week) and participants completed 30 minutes of multimodal cognitive training plus 45 minutes of moderate-intensity aerobic exercise (60-70% maximum heart rate). Participants in the aerobic exercise plus cognitive training group displayed increased working memory improvement in comparison to the active control group. Another trial designed a 12-week aerobic exercise training protocol, with added cognitive training beginning in the 6th week of treatment [143]. First, participants completed 30-minute sessions of aerobic exercise (3 times per week) and after 6 weeks, 30 minutes of computerized cognitive training (memory and attention) were added after the aerobic training period. The combined group had significant improvements in long and short-term verbal memory, cognitive flexibility, global and social functioning measures. Although there were no significant differences in improvements compared to the cognitive training plus table soccer group, the functional outcomes changes were correlated with enhanced cognitive functioning only in the combined training group. Moreover, a subsequent report regarding the same protocol found increased volume in the left superior, middle and inferior anterior temporal gyri after training [144]. Finally, a pilot study from Nuechterlein *et al.* [145] with first-episode schizophrenia patients engaged participants in combined aerobic exercise and cognitive training versus cognitive training alone. Over a 10 week period, participants completed 4 hours per week of cognitive training (neurocognitive plus social-cognitive exercises) and 150 minutes per week of aerobic exercise at 60-80% maximum heart rate (90 minutes in the clinic plus 60 minutes home-based). The combined intervention group was superior to the cognitive training alone on global cognition and independent living skills, with largest differential gains favoring the combined group on measures related to social cognition, working memory, processing speed and attention.

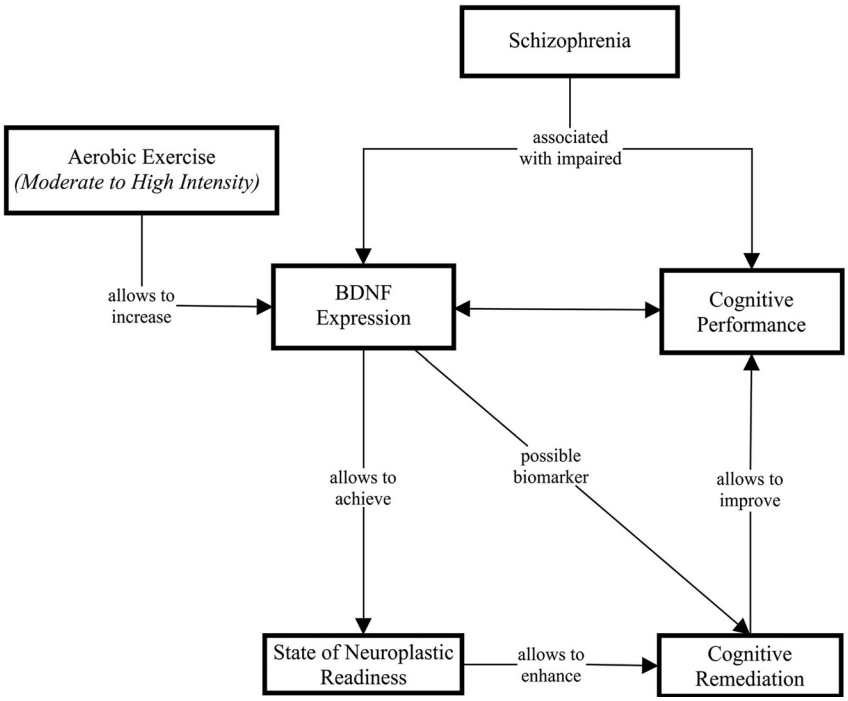

Fig. (1). Hypothesis of cognitive remediation efficacy enhancement for patients with schizophrenia through exercise-induced increase in BDNF levels.

Trials combining aerobic exercise with cognitive remediation are increasing and it seems clear that adding the effects of both interventions may allow to improve cognitive functioning. Furthermore, there are also a few trials exploring brain-related effects of combined exercise and cognitive remediation. Shah *et al.* [139] found an association between improved verbal memory and increased levels of cerebral glucose metabolism after a protocol of combined exercise and cognitive training for elderly participants. Combined training was associated with enhanced neural activity and BDNF could play a role in the detected changes, as there is evidence supporting the association between BDNF and glucose metabolism modulation [146, 147]. Furthermore, there is also evidence suggesting that combined aerobic and cognitive training can increase peripheral BDNF levels both in elderly participants [137] and in patients with schizophrenia [145].

Although there is still a need for further research regarding how BDNF mediates the interaction between exercise and cognitive remediation, the previously described findings contribute to our hypothesis, suggesting that exercise-induced BDNF levels increase before cognitive training can maximize its efficacy in patients with schizophrenia. The rationale behind this hypothesis is similar to the assumptions that underlie exercise usage to promote motor rehabilitation in stroke. Some authors suggest that BDNF can optimize neuroplastic potential and facilitate motor learning [148] and cognitive improvement [149] in order to promote the rehabilitative process. It is clear that neuroplasticity is a cornerstone of cognitive remediation and our hypothesis argues that exercise-induced plasticity, achieved by BDNF concentration increase, can enhance gains after the intervention. More specifically, engaging in aerobic exercise in close temporal proximity to cognitive remediation may allow achieving a state of neuroplastic readiness in the CNS [148, 150] as exercise-induced BDNF activity allows for a decrease in the threshold for successful encoding and memory [151]. This temporal closeness allows for the exercise-induced plastic effects to be more effectively harnessed during cognitive remediation, facilitating cognitive functioning enhancement [152].

Thereby, as temporal closeness between aerobic exercise and cognitive remediation may be critical to harness their combined effects, it's important to understand how BDNF levels fluctuate after a single bout of exercise. There is evidence suggesting that increased peripheral neurotrophin levels induced by exercise are incrementally cleared after exercise [153]. There is even consistent evidence stating that peripheral BDNF levels decrease back to baseline concentration within 15-60 minutes after exercise, regardless of exercise intensity [154]. Thereby, if cognitive remediation efficacy can be potentiated by exercise-induced BDNF levels increase, there is a considerably short time window for patients with schizophrenia to complete cognitive remediation procedures after aerobic exercise.

Another important issue when addressing the proposed hypothesis is to understand how aerobic exercise intensity plays a role on BDNF expression in schizophrenia. There has been evidence suggesting that the magnitude of BDNF increase is associated with exercise intensity [155, 156]. A systematic review from Knaepen *et al.* [154] including studies with healthy participants and patients with chronic diseases suggested that to immediately increase peripheral BDNF concentration participants should perform bouts of acute exercise at 60% maximum heart rate. The literature is scarce regarding the role of exercise intensity on BDNF

expression in patients with schizophrenia but evidence from both healthy and clinical populations suggest that moderate intensity can be reliable to increase peripheral BDNF levels [37]. Future studies should explore exercise protocols with different intensities to further understand the relationship between exercise and BDNF levels in this population.

To further support the proposed hypothesis it is also important to understand whether exercise-induced BDNF upregulation clearly occurs in the brain, promoting the neuroplastic mechanisms that support cognitive remediation. BDNF expression is usually measured by serum or plasma levels but it is important to understand if peripheral BDNF increase correlates to enhanced brain expression of this neurotrophin. BDNF release during exercise has been associated with several sources including platelets [stores most of the peripheral BDNF; 157] and skeletal muscle cells [BDNF is produced by these cells in response to contraction; 158]. However, Rasmussen *et al.* [159] findings suggest that the brain is the main provider of circulating BDNF after exercise, contributing around 70-80% of total production. Furthermore, although some authors argue that BDNF does not easily cross the blood-brain barrier (BBB); [160], there has evidence suggesting that BDNF in the peripheral circulation can cross the BBB by a high-capacity, saturable transport system [161, 162], a process which is likely enhanced after exercise as there is increased BBB permeability [163, 164]. Thereby, it seems that BDNF can cross the BBB bidirectionally, allowing to hypothesize that BDNF leaves the brain in order to be stored in other body regions or that peripheral BDNF is transported to the brain in order to promote neural health [165]. Either way, although the mechanisms of exercise-induced BDNF expression are not perfectly understood, it seems that this neurotrophin is clearly related to brain neuroplasticity after exercise or at least an important indicator of enhanced neuroplastic activity.

Finally, it is also important to debate the practical implications of sequentially performing aerobic exercise plus cognitive remediation. Adherence is a challenge for any intervention targeting patients with schizophrenia. Moderate attendance rates have been described in programs using aerobic exercise alone [166] and these values could be even lower in more demanding protocols such as combined exercise and cognitive remediation. Most studies combining these interventions do not provide clear information regarding the timeline between cognitive remediation and aerobic exercise sessions, but most of them seem to provide the interventions on different days. Interestingly, in the study from Malchow *et al.* [143] participants actually completed cognitive remediation right after the aerobic exercise period and had a positive adherence to the protocol. Only 3 participants dropped out of the study and the remaining 22 completed 75% or more of the training sessions. Thereby, it seems feasible to combine both interventions consecutively although future trials should explore resources to promote long-term protocol adherence. For instance, exergames have been used to engage patients with schizophrenia in physical activity [167, 168] and designing games that allow participants to accomplish both aerobic exercise and cognitive remediation may be an interesting resource to increase participant's adherence. Group based aerobic exercise may also be a valuable resource to engage patients with schizophrenia as social support plays a critical role in initiating and maintaining compliance to exercise [169].

Finally, an alternative pathway to promote exercise-induced neuroplasticity may be the long-term increase in BDNF levels achieved by regular exercise. A recent meta-analysis reported that prolonged exercise programs ranging from 3 weeks to 2 years, with a frequency of 2 to 5 days per week were able to effectively increase resting peripheral BDNF levels [37]. Moreover, the authors also reported that when engaging in regular physical exercise, there is an increase in neurotrophic activity that becomes gradually larger after each training session. Thereby, one can postulate that cognitive remediation efficacy for patients with schizophrenia may be enhanced if participants previously engage in aerobic exercise training, in order to create a state of neuroplastic readiness in the brain. There are no guidelines regarding the frequency or duration needed in order to achieve brain plasticity benefits, but it seems reasonable to follow the international exercise recommendations which state that patients should do at least 150 minutes a week of moderate-intensity, or 75 minutes of moderate- to vigorous-intensity aerobic activity [170, 171].

CONCLUSION

Cognitive remediation's biological validity is clearly related to the structural and functional brain changes achieved through the neuroplasticity mechanisms that underlie learning and cognitive functioning improvements. Aerobic exercise may be an effective tool to enhance this plasticity by up-regulating BDNF expression, a neurothopin which is directly involved in learning and memory. Thereby, the development of cognitive remediation sessions shortly after single bouts of aerobic exercise should allow for a neural environment that nurtures the efficacy on cognitive outcomes. There is still a need to design high-quality clinical trials assessing the role of exercise intensity on BDNF levels increase in schizophrenia. Furthermore, it would be interesting to understand if baseline BDNF levels predict cognitive remediation outcomes as there are no studies reporting this association. Finally, the temporal relationship when combining cognitive remediation and aerobic exercise should be explored, to understand the processes behind the cumulative effects of both interventions.

Cognitive deficits present a major burden for patients with schizophrenia and their families. Due to the inefficiency of pharmacological treatment in the treatment of these deficits, enhancing the efficacy of cognitive remediation through exercise-induced plasticity can be an appealing and effective alternative. There are several factors that play of role on neuroplasticity such as demographic variables, clinical history, pharmacological treatment, genetic factors, among others. However, future clinical trials using cognitive remediation for schizophrenia should be designed to explore possible strategies to maximize neuroplasticity and, thereby, achieve optimal cognitive improvements.

LIST OF ABBREVIATIONS

BDNF	=	Brain-Derived Neurotrophic Factor
BBB	=	Blood-Brain Barrier

fMRI = Functional Magnetic Resonance Imaging
mRNA = Messenger Ribonucleic Acid
PFC = Prefrontal Cortex

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none

REFERENCES

[1] Kahn RS, Keefe RS. Schizophrenia is a cognitive illness: time for a change in focus. JAMA Psychiatry 2013; 70(10): 1107-12.
[2] Joyce EM, Hutton SB, Mutsatsa SH, Barnes TR. Cognitive heterogeneity in first-episode schizophrenia. Br J Psychiatry 2005; 187: 516-22.
[3] Nuechterlein KH, Subotnik KL, Green MF, *et al*. Neurocognitive predictors of work outcome in recent-onset schizophrenia. Schizophr Bull 2011; 37(2): S33-40.
[4] Bowie CR, Harvey PD. Cognitive deficits and functional outcome in schizophrenia. Neuropsychiatr Dis Treat 2006; 2(4): 531-6.
[5] Lepage M, Bodnar M, Bowie CR. Neurocognition: clinical and functional outcomes in schizophrenia. Can J Psychiatry 2014; 59(1): 5-12.
[6] Dawes SE, Jeste DV, Palmer BW. Cognitive profiles in persons with chronic schizophrenia. J Clin Exp Neuropsychol 2011; 33(8): 929-36.
[7] Palmer BW, Dawes SE, Heaton RK. What do we know about neuropsychological aspects of schizophrenia? Neuropsychol Rev 2009; 19(3): 365-84.
[8] Corigliano V, De Carolis A, Trovini G, *et al*. Neurocognition in schizophrenia: from prodrome to multi-episode illness. Psychiatry Res 2014; 220(1-2): 129-34.
[9] Nuechterlein KH, Barch DM, Gold JM, Goldberg TE, Green MF, Heaton RK. Identification of separable cognitive factors in schizophrenia. Schizophr Res 2004; 72(1): 29-39.
[10] Savla GN, Vella L, Armstrong CC, Penn DL, Twamley EW. Deficits in domains of social cognition in schizophrenia: a meta-analysis of the empirical evidence. Schizophr Bull 2013; 39(5): 979-92.
[11] Davidson M, Galderisi S, Weiser M, *et al*. Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: a randomized, open-label clinical trial (EUFEST). Am J Psychiatry 2009; 166(6): 675-82.
[12] Keefe RS, Bilder RM, Davis SM, *et al*. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. Arch Gen Psychiatry 2007; 64(6): 633-47.
[13] Thorsen AL, Johansson K, Løberg EM. Neurobiology of cognitive remediation therapy for schizophrenia: a systematic review. Front Psychiatry 2014; 5: 103.
[14] Saperstein AM, Kurtz MM. Current trends in the empirical study of cognitive remediation for schizophrenia. Can J Psychiatry 2013; 58(6): 311-8.
[15] Wykes T, Spaulding WD. Thinking about the future cognitive remediation therapy-what works and could we do better? Schizophr Bull 2011; 37 Suppl 2: S80-90.
[16] Kurtz MM, Moberg PJ, Gur RC, Gur RE. Approaches to cognitive remediation of neuropsychological deficits in schizophrenia: a review and meta-analysis. Neuropsychol Rev 2001; 11(4): 197-210.
[17] Grynszpan O, Perbal S, Pelissolo A, *et al*. Efficacy and specificity of computer-assisted cognitive remediation in schizophrenia: a meta-analytical study. Psychol Med 2011; 41(1): 163-73.
[18] McGurk SR, Twamley EW, Sitzer DI, McHugo GJ, Mueser KT. A meta-analysis of cognitive remediation in schizophrenia. Am J Psychiatry 2007; 164(12): 1791-802.
[19] Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. Am J Psychiatry 2011; 168(5): 472-85.
[20] Kurtz MM, Richardson CL. Social cognitive training for schizophrenia: a meta-analytic investigation of controlled research. Schizophr Bull 2012; 38(5): 1092-04.
[21] Kurtz MM, Gagen E, Rocha NB, Machado S, Penn DL. Comprehensive treatments for social cognitive deficits in schizophrenia: a critical review and effect-size analysis of controlled studies. Clin Psychol Rev 2016; 43: 80-9.
[22] Medalia A, Choi J. Cognitive remediation in schizophrenia. Neuropsychol Rev 2009; 19(3): 353-64.
[23] Barlati S, Deste G, De Peri L, Ariu C, Vita A. Cognitive remediation in schizophrenia: current status and future perspectives. Schizophr Res Treatment 2013; 2013: 156084.
[24] Kurtz MM. Cognitive remediation for schizophrenia: current status, biological correlates and predictors of response. Expert Rev Neurother 2012; 12(7): 813-21.
[25] Lett TA, Voineskos AN, Kennedy JL, Levine B, Daskalakis ZJ. Treating working memory deficits in schizophrenia: a review of the neurobiology. Biol Psychiatry 2014; 75(5): 361-70.
[26] Vinogradov S, Fisher M, Holland C, Shelly W, Wolkowitz O, Mellon SH. Is serum brain-derived neurotrophic factor a biomarker for cognitive enhancement in schizophrenia? Biol Psychiatry 2009; 66(6): 549-53.
[27] Angelucci F, Peppe A, Carlesimo GA, *et al*. A pilot study on the effect of cognitive training on BDNF serum levels in individuals with Parkinson's disease. Front Hum Neurosci 2015; 9: 130.
[28] Leal G, Afonso PM, Salazar IL, Duarte CB. Regulation of hippocampal synaptic plasticity by BDNF. Brain Res 2014.
[29] Lewin GR, Barde YA. Physiology of the neurotrophins. Ann Rev Neurosci 1996; 19: 289-17.
[30] Lu B, Pang PT, Woo NH. The yin and yang of neurotrophin action. Nat Rev Neurosci 2005; 6(8): 603-14.
[31] Gorski JA, Zeiler SR, Tamowski S, Jones KR. Brain-derived neurotrophic factor is required for the maintenance of cortical dendrites. J Neurosci 2003; 23(17): 6856-65.
[32] Favalli G, Li J, Belmonte-de-Abreu P, Wong AH, Daskalakis ZJ. The role of BDNF in the pathophysiology and treatment of schizophrenia. J Psychiatr Res 2012; 46(1): 1-11.
[33] Zheng G, Xia R, Zhou W, Tao J, Chen L. Aerobic exercise ameliorates cognitive function in older adults with mild cognitive impairment: a systematic review and meta-analysis of randomised controlled trials. Br J Sports Med 2016.
[34] Groot C, Hooghiemstra AM, Raijmakers PG, *et al*. The effect of physical activity on cognitive function in patients with dementia: a meta-analysis of randomized control trials. Ageing Res Rev 2016; 25: 13-23.
[35] García-Soto E, López de Munaín ML, Santibáñez M. Effects of combined aerobic and resistance training on cognition following stroke: a systematic review. Rev Neurol 2013; 57(12): 535-41.
[36] Roig M, Nordbrandt S, Geertsen SS, Nielsen JB. The effects of cardiovascular exercise on human memory: a review with meta-analysis. Neurosci Biobehav Rev 2013; 37(8): 1645-66.
[37] Szuhany KL, Bugatti M, Otto MW. A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. J Psychiatr Res 2014; 60C: 56-64.
[38] Law LL, Barnett F, Yau MK, Gray MA. Effects of combined cognitive and exercise interventions on cognition in older adults with and without cognitive impairment: a systematic review. Ageing Res Rev 2014; 15: 61-75.
[39] Motl RW, Sandroff BM, DeLuca J. Exercise training and cognitive rehabilitation: a symbiotic approach for rehabilitating walking and cognitive functions in multiple sclerosis. Neurorehabil Neural Repair 2016; 30(6): 499-11.
[40] Livingston-Thomas J, Nelson P, *et al*. Exercise and environmental enrichment as enablers of task-specific neuroplasticity and stroke recovery. Neurotherapeutics 2016; 13(2): 395-02.
[41] Zhu X, Yin S, Lang M, He R, Li J. The more the better? A meta-analysis on effects of combined cognitive and physical intervention on cognition in healthy older adults. Ageing Res Rev 2016; 31: 67-79.
[42] Wei YY, Wang JJ, Yan C, *et al*. Correlation between brain activation changes and cognitive improvement following cognitive remediation therapy in schizophrenia: an activation likelihood estimation meta-analysis. Chin Med J (Engl) 2016; 129(5): 578-85.
[43] Campos C, Santos S, Gagen E, *et al*. Neuroplastic changes following social cognition training in schizophrenia: a systematic review. Neuropsychol Rev 2016.

[44] Wykes T, Brammer M, Mellers J, *et al*. Effects on the brain of a psychological treatment: cognitive remediation therapy: functional magnetic resonance imaging in schizophrenia. Br J Psychiatry 2002; 181: 144-52.

[45] Bor J, Brunelin J, d'Amato T, *et al*. How can cognitive remediation therapy modulate brain activations in schizophrenia? An fMRI study. Psychiatry Res 2011; 192(3): 160-6.

[46] Subramaniam K, Luks TL, Garrett C, *et al*. Intensive cognitive training in schizophrenia enhances working memory and associated prefrontal cortical efficiency in a manner that drives long-term functional gains. Neuroimage 2014; 99: 281-92.

[47] Subramaniam K, Luks TL, Fisher M, Simpson GV, Nagarajan S, Vinogradov S. Computerized cognitive training restores neural activity within the reality monitoring network in schizophrenia. Neuron 2012; 73(4): 842-53.

[48] Haut KM, Lim KO, MacDonald A. Prefrontal cortical changes following cognitive training in patients with chronic schizophrenia: effects of practice, generalization, and specificity. Neuropsychopharmacology 2010; 35(9): 1850-9.

[49] Wexler BE, Anderson M, Fulbright RK, Gore JC. Preliminary evidence of improved verbal working memory performance and normalization of task-related frontal lobe activation in schizophrenia following cognitive exercises. Am J Psychiatry 2000; 157(10): 1694-7.

[50] Pu S, Nakagome K, Yamada T, *et al*. A pilot study on the effects of cognitive remediation on hemodynamic responses in the prefrontal cortices of patients with schizophrenia: a multi-channel near-infrared spectroscopy study. Schizophr Res 2014; 153(1-3): 87-95.

[51] Vianin P, Urben S, Magistretti P, Marquet P, Fornari E, Jaugey L. Increased activation in Broca's area after cognitive remediation in schizophrenia. Psychiatry Res 2014; 221(3): 204-9.

[52] Hooker CI, Bruce L, Fisher M, Verosky SC, Miyakawa A, Vinogradov S. Neural activity during emotion recognition after combined cognitive plus social cognitive training in schizophrenia. Schizophr Res 2012; 139(1-3): 53-9.

[53] Hooker CI, Bruce L, Fisher M, *et al*. The influence of combined cognitive plus social-cognitive training on amygdala response during face emotion recognition in schizophrenia. Psychiatry Res 2013; 213(2): 99-107.

[54] Adcock RA, Dale C, Fisher M, *et al*. When top-down meets bottom-up: auditory training enhances verbal memory in schizophrenia. Schizophr Bull 2009; 35(6): 1132-41.

[55] Popov T, Jordanov T, Rockstroh B, Elbert T, Merzenich MM, Miller GA. Specific cognitive training normalizes auditory sensory gating in schizophrenia: a randomized trial. Biol Psychiatry 2011; 69(5): 465-71.

[56] Popov T, Rockstroh B, Weisz N, Elbert T, Miller GA. Adjusting brain dynamics in schizophrenia by means of perceptual and cognitive training. PLoS One 2012; 7(7): e39051.

[57] Luckhaus C, Frommann N, Stroth S, Brinkmeyer J, Wölwer W. Training of affect recognition in schizophrenia patients with violent offences: behavioral treatment effects and electrophysiological correlates. Soc Neurosci 2013; 8(5): 505-14.

[58] Rass O, Forsyth JK, Bolbecker AR, *et al*. Computer-assisted cognitive remediation for schizophrenia: a randomized single-blind pilot study. Schizophr Res 2012; 139(1-3): 92-8.

[59] Eack SM, Hogarty GE, Cho RY, *et al*. Neuroprotective effects of cognitive enhancement therapy against gray matter loss in early schizophrenia: results from a 2-year randomized controlled trial. Arch Gen Psychiatry. 2010; 67(7): 674-82.

[60] Penadés R, Pujol N, Catalán R, *et al*. Brain effects of cognitive remediation therapy in schizophrenia: a structural and functional neuroimaging study. Biol Psychiatry 2013; 73(10): 1015-23.

[61] Bekinschtein P, Cammarota M, Medina JH. BDNF and memory processing. Neuropharmacology 2014; 76 Pt C: 677-83.

[62] Bekinschtein P, Oomen CA, Saksida LM, Bussey TJ. Effects of environmental enrichment and voluntary exercise on neurogenesis, learning and memory, and pattern separation: BDNF as a critical variable? Sem cell development biol 2011; 22(5): 536-42.

[63] Alonso M, Medina JH, Pozzo-Miller L. ERK1/2 activation is necessary for BDNF to increase dendritic spine density in hippocampal CA1 pyramidal neurons. Learn memory 2004; 11(2): 172-8.

[64] Leuner B, Falduto J, Shors TJ. Associative memory formation increases the observation of dendritic spines in the hippocampus. J Neurosci 2003; 23(2): 659-65.

[65] Monteggia LM, Barrot M, Powell CM, *et al*. Essential role of brain-derived neurotrophic factor in adult hippocampal function. Proc Nat Acad Sci USA 2004; 101(29): 10827-32.

[66] Heldt SA, Stanek L, Chhatwal JP, Ressler KJ. Hippocampus-specific deletion of BDNF in adult mice impairs spatial memory and extinction of aversive memories. Mol Psychiatry 2007; 12(7): 656-70.

[67] Furini CR, Rossato JI, Bitencourt LL, Medina JH, Izquierdo I, Cammarota M. Beta-adrenergic receptors link NO/sGC/PKG signaling to BDNF expression during the consolidation of object recognition long-term memory. Hippocampus. 2010; 20(5): 672-83.

[68] Sakata K, Martinowich K, Woo NH, *et al*. Role of activity-dependent BDNF expression in hippocampal-prefrontal cortical regulation of behavioral perseverance. Proc Natl Acad Sci USA. 2013; 110(37): 15103-8.

[69] Koponen E, Võikar V, Riekki R, *et al*. Transgenic mice overexpressing the full-length neurotrophin receptor trkB exhibit increased activation of the trkB-PLCgamma pathway, reduced anxiety, and facilitated learning. Mol Cell Neurosci 2004; 26(1): 166-81.

[70] D'Amore DE, Tracy BA, Parikh V. Exogenous BDNF facilitates strategy set-shifting by modulating glutamate dynamics in the dorsal striatum. Neuropharmacology 2013; 75: 312-23.

[71] Savitz J, Solms M, Ramesar R. The molecular genetics of cognition: dopamine, COMT and BDNF. Genes Brain Behav 2006; 5(4): 311-28.

[72] Egan MF, Kojima M, Callicott JH, *et al*. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 2003; 112(2): 257-69.

[73] Hariri AR, Goldberg TE, Mattay VS, *et al*. Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. J Neurosci 2003; 23(17): 6690-4.

[74] Alfimova MV, Korovaitseva GI, Lezheiko TV, Golimbet VE. Effect of BDNF Val66Met polymorphism on normal variability of executive functions. Bull Exp Biol Med 2012; 152(5): 606-9.

[75] Tükel R, Gürvit H, Ozata B, *et al*. Brain-derived neurotrophic factor gene Val66Met polymorphism and cognitive function in obsessive-compulsive disorder. Am J Med Genet B Neuropsychiatr Genet 2012; 159(7): 850-8.

[76] Koven KS, Carr LH. The role of the brain-derived neurotrophic factor c270t polymorphism in executive functioning. Journal of Applied Medical Sciences 2013; 2(1): 25-41.

[77] Ickes BR, Pham TM, Sanders LA, Albeck DS, Mohammed AH, Granholm AC. Long-term environmental enrichment leads to regional increases in neurotrophin levels in rat brain. Exp Neurol 2000; 164(1): 45-52.

[78] Angelucci F, De Bartolo P, Gelfo F, *et al*. Increased concentrations of nerve growth factor and brain-derived neurotrophic factor in the rat cerebellum after exposure to environmental enrichment. Cerebellum. 2009; 8(4): 499-06.

[79] Novkovic T, Mittmann T, Manahan-Vaughan D. BDNF contributes to the facilitation of hippocampal synaptic plasticity and learning enabled by environmental enrichment. Hippocampus 2015; 25(1): 1-15.

[80] Rossi C, Angelucci A, Costantin L, *et al*. Brain-derived neurotrophic factor (BDNF) is required for the enhancement of hippocampal neurogenesis following environmental enrichment. Eur J Neurosci 2006; 24(7): 1850-6.

[81] Ramírez-Rodríguez G, Ocaña-Fernández MA, Vega-Rivera NM, *et al*. Environmental enrichment induces neuroplastic changes in middle age female Balb/c mice and increases the hippocampal levels of BDNF, p-Akt and p-MAPK1/2. Neuroscience 2014; 260: 158-70.

[82] Falkenberg T, Mohammed AK, Henriksson B, Persson H, Winblad B, Lindefors N. Increased expression of brain-derived neurotrophic factor mRNA in rat hippocampus is associated with improved spatial memory and enriched environment. Neurosci Lett 1992; 138(1): 153-6.

[83] Anomal R, de Villers-Sidani E, Merzenich MM, Panizzutti R. Manipulation of BDNF signaling modifies the experience-dependent plasticity induced by pure tone exposure during the critical period in the primary auditory cortex. PLoS One 2013; 8(5): e64208.

[84] Casoli T, Giuli C, Balietti M, Giorgetti B, Solazzi M, Fattoretti P. Effect of cognitive training on the expression of brain-derived neurotrophic factor in lymphocytes of mild cognitive impairment patients. Rejuvenation Res 2014; 17(2): 235-8.

[85] Pressler SJ, Titler M, Koelling TM, *et al*. Nurse-enhanced computerized cognitive training increases serum brain-derived neurotropic factor levels and improves working memory in heart failure. J Card Fail 2015; 21(8): 630-41.

[86] Fisher M, Mellon SH, Wolkowitz O, Vinogradov S. Neuroscience-informed auditory training in schizophrenia: a final report of the effects on cognition and serum brain-derived neurotrophic factor. Schizophr Res Cogn 2016; 3: 1-7.

[87] Mak M, Samochowiec J, Tybura P, *et al*. The efficacy of cognitive rehabilitation with Reha Com programme in schizophrenia patients. The role of selected genetic polymorphisms in successful cognitive rehabilitation. Ann Agric Environ Med 2013; 20(1): 77-81.

[88] Kuo FC, Lee CH, Hsieh CH, Kuo P, Chen YC, Hung YJ. Lifestyle modification and behavior therapy effectively reduce body weight and increase serum level of brain-derived neurotrophic factor in obese non-diabetic patients with schizophrenia. Psychiatry Res 2013; 209(2): 150-4.

[89] Notaras M, Hill R, van den Buuse M. A role for the bdnf gene val66met polymorphism in schizophrenia? A comprehensive review. Neurosci Bio Behav Rev 2015.

[90] Jönsson EG, Edman-Ahlbom B, Sillén A, *et al*. Brain-derived neurotrophic factor gene (BDNF) variants and schizophrenia: an association study. Prog Neuropsychopharmacol Biol Psychiatry 2006; 30(5): 924-33.

[91] Naoe Y, Shinkai T, Hori H, *et al*. No association between the brain-derived neurotrophic factor (BDNF) Val66Met polymorphism and schizophrenia in Asian populations: Evidence from a case-control study and meta-analysis. Neurosci Lett 2007; 415(2): 108-12.

[92] Kawashima K, Ikeda M, Kishi T, *et al*. BDNF is not associated with schizophrenia: data from a Japanese population study and meta-analysis. Schizophr Res 2009; 112(1-3): 72-9.

[93] Nieto R, Kukuljan M, Silva H. BDNF and schizophrenia: from neurodevelopment to neuronal plasticity, learning, and memory. Front Psychiatry 2013; 4: 45.

[94] Lu W, Zhang C, Yi Z, Li Z, Wu Z, Fang Y. Association between BDNF Val66Met polymorphism and cognitive performance in antipsychotic-naïve patients with schizophrenia. J Mol Neurosci 2012; 47(3): 505-10.

[95] Zhang XY, Chen dC, Xiu MH, *et al*. Cognitive and serum BDNF correlates of BDNF Val66Met gene polymorphism in patients with schizophrenia and normal controls. Hum Genet 2012; 131(7): 1187-95.

[96] Rybakowski JK, Borkowska A, Skibinska M, *et al*. Prefrontal cognition in schizophrenia and bipolar illness in relation to Val66Met polymorphism of the brain-derived neurotrophic factor gene. Psychiatry Clin Neurosci 2006; 60(1): 70-6.

[97] Eisenberg DP, Ianni AM, Wei SM, *et al*. Brain-derived neurotrophic factor (BDNF) Val(66)Met polymorphism differentially predicts hippocampal function in medication-free patients with schizophrenia. Mol Psychiatry. 2013; 18(6): 713-20.

[98] Durany N, Michel T, Zöchling R, *et al*. Brain-derived neurotrophic factor and neurotrophin 3 in schizophrenic psychoses. Schizophr Res 2001; 52(1-2): 79-86.

[99] Takahashi M, Shirakawa O, Toyooka K, *et al*. Abnormal expression of brain-derived neurotrophic factor and its receptor in the corticolimbic system of schizophrenic patients. Mol Psychiatry 2000; 5(3): 293-300.

[100] Hashimoto T, Bergen SE, Nguyen QL, *et al*. Relationship of brain-derived neurotrophic factor and its receptor TrkB to altered inhibitory prefrontal circuitry in schizophrenia. J Neurosci 2005; 25(2): 372-83.

[101] Issa G, Wilson C, Terry AV, Jr., Pillai A. An inverse relationship between cortisol and BDNF levels in schizophrenia: data from human postmortem and animal studies. Neurobiol Dis 2010; 39(3): 327-33.

[102] Weickert CS, Hyde TM, Lipska BK, Herman MM, Weinberger DR, Kleinman JE. Reduced brain-derived neurotrophic factor in prefrontal cortex of patients with schizophrenia. Mol Psychiatry 2003; 8(6): 592-10.

[103] Green MJ, Matheson SL, Shepherd A, Weickert CS, Carr VJ. Brain-derived neurotrophic factor levels in schizophrenia: a systematic review with meta-analysis. Mol Psychiatry 2011; 16(9): 960-72.

[104] Fernandes BS, Steiner J, Berk M, *et al*. Peripheral brain-derived neurotrophic factor in schizophrenia and the role of antipsychotics: meta-analysis and implications. Mol Psychiatry 2014.

[105] Huang TL, Lee CT. Associations between serum brain-derived neurotrophic factor levels and clinical phenotypes in schizophrenia patients. J Psychiatr Res 2006; 40(7): 664-8.

[106] Zhang XY, Tan YL, Zhou DF, *et al*. Serum BDNF levels and weight gain in schizophrenic patients on long-term treatment with antipsychotics. J Psychiatr Res 2007; 41(12): 997-04.

[107] Shimizu E, Hashimoto K, Watanabe H, *et al*. Serum brain-derived neurotrophic factor (BDNF) levels in schizophrenia are indistinguishable from controls. Neurosci Lett 2003; 351(2): 111-4.

[108] Reis HJ, Nicolato R, Barbosa IG, Teixeira do Prado PH, Romano-Silva MA, Teixeira AL. Increased serum levels of brain-derived neurotrophic factor in chronic institutionalized patients with schizophrenia. Neurosci Lett 2008; 439(2): 157-9.

[109] Niitsu T, Shirayama Y, Matsuzawa D, *et al*. Associations of serum brain-derived neurotrophic factor with cognitive impairments and negative symptoms in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2011; 35(8): 1836-40.

[110] Carlino D, Leone E, Di Cola F, *et al*. Low serum truncated-BDNF isoform correlates with higher cognitive impairment in schizophrenia. J Psychiatr Res 2011; 45(2): 273-9.

[111] Zhang XY, Chen DC, Tan YL, *et al*. Gender difference in association of cognition with BDNF in chronic schizophrenia. Psychoneuroendocrinology 2014; 48: 136-46.

[112] Ruiz de Azua S, Matute C, Stertz L, *et al*. Plasma brain-derived neurotrophic factor levels, learning capacity and cognition in patients with first episode psychosis. BMC Psychiatry 2013; 13: 27.

[113] Rizos EN, Papathanasiou M, Michalopoulou PG, *et al*. Association of serum BDNF levels with hippocampal volumes in first psychotic episode drug-naive schizophrenic patients. Schizophr Res 2011; 129(2-3): 201-4.

[114] Wobrock T, Hasan A, Falkai P. Innovative treatment approaches in schizophrenia enhancing neuroplasticity: aerobic exercise, erythropoetin and repetitive transcranial magnetic stimulation. Curr Pharm Biotechnol 2012; 13(8): 1595-605.

[115] Rimes RR, de Souza Moura AM, Lamego MK, *et al*. Effects of exercise on physical and mental health, and cognitive and brain functions in schizophrenia: clinical and experimental evidence. CNS Neurol Disord Drug Targets 2015; 14(10): 1244-54.

[116] Vancampfort D, Probst M, De Hert M, *et al*. Neurobiological effects of physical exercise in schizophrenia: a systematic review. Disabil Rehabil 2014; 36(21): 1749-54.

[117] Zwick S, Brunnauer A, Laux G. Effects of aerobic endurance training on neurocognitive function in schizophrenic patients. 18th European Congress of Psychiatry; Munich, Germany2010. p. 1136.

[118] Falkai P, Malchow B, Wobrock T, *et al*. The effect of aerobic exercise on cortical architecture in patients with chronic schizophrenia: a randomized controlled MRI study. Eur Arch Psychiatry Clin Neurosci 2013; 263(6): 469-73.

[119] Strassnig MT, Signorile JF, Potiaumpai M, *et al*. High velocity circuit resistance training improves cognition, psychiatric symptoms and neuromuscular performance in overweight outpatients with severe mental illness. Psychiatry Res 2015; 229(1-2): 295-301.

[120] Pajonk FG, Wobrock T, Gruber O, *et al*. Hippocampal plasticity in response to exercise in schizophrenia. Arch Gen Psychiatry. 2010; 67(2): 133-43.

[121] Scheewe TW, van Haren NE, Sarkisyan G, *et al*. Exercise therapy, cardiorespiratory fitness and their effect on brain volumes: a randomised controlled trial in patients with schizophrenia and healthy controls. Eur Neuropsychopharmacol 2013; 23(7): 675-85.

[122] Svatkova A, Mandl RC, Scheewe TW, Cahn W, Kahn RS, Hulshoff Pol HE. Physical exercise keeps the brain connected: biking increases white matter integrity in patients with schizophrenia and healthy controls. Schizophr Bull 2015; 41(4): 869-78.

[123] Neeper SA, Gómez-Pinilla F, Choi J, Cotman C. Exercise and brain neurotrophins. Nature 1995; 373(6510): 109.

[124] Vaynman S, Ying Z, Gomez-Pinilla F. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. Eur J Neurosci 2004; 20(10): 2580-90.

[125] Zoladz JA, Pilc A. The effect of physical activity on the brain derived neurotrophic factor: from animal to human studies. J Physiol Pharmacol 2010; 61(5): 533-41.
[126] Huang T, Larsen KT, Ried-Larsen M, Møller NC, Andersen LB. The effects of physical activity and exercise on brain-derived neurotrophic factor in healthy humans: A review. Scand J Med Sci Sports 2014; 24(1): 1-10.
[127] Gustafsson G, Lira CM, Johansson J, *et al*. The acute response of plasma brain-derived neurotrophic factor as a result of exercise in major depressive disorder. Psychiatry Res 2009; 169(3): 244-8.
[128] Laske C, Banschbach S, Stransky E, *et al*. Exercise-induced normalization of decreased BDNF serum concentration in elderly women with remitted major depression. Int J Neuropsychopharmacol 2010; 13(5): 595-02.
[129] Toups MS, Greer TL, Kurian BT, *et al*. Effects of serum Brain Derived Neurotrophic Factor on exercise augmentation treatment of depression. J Psychiatr Res 2011; 45(10): 1301-6.
[130] Ströhle A. Physical activity, exercise, depression and anxiety disorders. J Neural Transm. 2009; 116(6): 777-84.
[131] Baker LD, Frank LL, Foster-Schubert K, *et al*. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. Arch Neurol 2010; 67(1): 71-9.
[132] Coelho FG, Vital TM, Stein AM, *et al*. Acute aerobic exercise increases brain-derived neurotrophic factor levels in elderly with Alzheimer's disease. J Alzheimers Dis 2014; 39(2): 401-8.
[133] Kim HJ, Song BK, So B, Lee O, Song W, Kim Y. Increase of circulating BDNF levels and its relation to improvement of physical fitness following 12 weeks of combined exercise in chronic patients with schizophrenia: a pilot study. Psychiatry Res 2014; 220(3): 792-6.
[134] Kimhy D, Vakhrusheva J, Bartels MN, *et al*. The impact of aerobic exercise on brain-derived neurotrophic factor and neurocognition in individuals with schizophrenia: a single-blind, randomized clinical trial. Schizophr Bull 2015; 41(4): 859-68.
[135] Lauenroth A, Ioannidis AE, Teichmann B. Influence of combined physical and cognitive training on cognition: a systematic review. BMC Geriatr 2016; 16: 141.
[136] van het Reve E, de Bruin ED. Strength-balance supplemented with computerized cognitive training to improve dual task gait and divided attention in older adults: a multicenter randomized-controlled trial. BMC Geriatr 2014; 14: 134.
[137] Rahe J, Petrelli A, Kaesberg S, Fink GR, Kessler J, Kalbe E. Effects of cognitive training with additional physical activity compared to pure cognitive training in healthy older adults. Clin Interv Aging 2015; 10: 297-10.
[138] Eggenberger P, Schumacher V, Angst M, Theill N, de Bruin ED. Does multicomponent physical exercise with simultaneous cognitive training boost cognitive performance in older adults? A 6-month randomized controlled trial with a 1-year follow-up. Clin Interv Aging 2015; 10: 1335-49.
[139] Shah T, Verdile G, Sohrabi H, *et al*. A combination of physical activity and computerized brain training improves verbal memory and increases cerebral glucose metabolism in the elderly. Transl Psychiatry 2014; 4: e487.
[140] Fabre C, Chamari K, Mucci P, Massé-Biron J, Préfaut C. Improvement of cognitive function by mental and/or individualized aerobic training in healthy elderly subjects. Int J Sports Med 2002; 23(6): 415-21.
[141] Oswald WD, Gunzelmann T, Rupprecht R, Hagen B. Differential effects of single versus combined cognitive and physical training with older adults: the SimA study in a 5-year perspective. Eur J Ageing 2006; 3: 179-92.
[142] Oertel-Knöchel V, Mehler P, Thiel C, *et al*. Effects of aerobic exercise on cognitive performance and individual psychopathology in depressive and schizophrenia patients. Eur Arch Psychiatry Clin Neurosci 2014; 264(7): 589-04.
[143] Malchow B, Keller K, Hasan A, *et al*. Effects of endurance training combined with cognitive remediation on everyday functioning, symptoms, and cognition in multiepisode schizophrenia patients. Schizophr Bull 2015; 41(4): 847-58.
[144] Malchow B, Keeser D, Keller K, *et al*. Effects of endurance training on brain structures in chronic schizophrenia patients and healthy controls. Schizophr Res 2016; 173(3):182-91.
[145] Nuechterlein KH, Ventura J, McEwen SC, Gretchen-Doorly D, Vinogradov S, Subotnik KL. Enhancing cognitive training through aerobic exercise after a first schizophrenia episode: theoretical conception and pilot study. Schizophr Bull 2016; 42 Suppl 1: S44-52.
[146] Marosi K, Mattson MP. BDNF mediates adaptive brain and body responses to energetic challenges. Trends in endocrinology and metabolism: TEM 2014; 25(2): 89-98.
[147] Burkhalter J, Fiumelli H, Allaman I, Chatton JY, Martin JL. Brain-derived neurotrophic factor stimulates energy metabolism in developing cortical neurons. J Neurosci 2003; 23(23): 8212-20.
[148] Mang CS, Campbell KL, Ross CJ, Boyd LA. Promoting neuroplasticity for motor rehabilitation after stroke: considering the effects of aerobic exercise and genetic variation on brain-derived neurotrophic factor. Phys Ther 2013; 93(12): 1707-16.
[149] Griesbach GS, Hovda DA, Gomez-Pinilla F. Exercise-induced improvement in cognitive performance after traumatic brain injury in rats is dependent on BDNF activation. Brain Res 2009; 1288: 105-15.
[150] Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends Neurosci 2007; 30(9): 464-72.
[151] Intlekofer KA, Berchtold NC, Malvaez M, *et al*. Exercise and sodium butyrate transform a subthreshold learning event into long-term memory *via* a brain-derived neurotrophic factor-dependent mechanism. Neuropsychopharmacology 2013; 38(10): 2027-34.
[152] Lambourne K, Tomporowski P. The effect of exercise-induced arousal on cognitive task performance: a meta-regression analysis. Brain Res 2010; 1341: 12-24.
[153] Berchtold NC, Chinn G, Chou M, Kesslak JP, Cotman CW. Exercise primes a molecular memory for brain-derived neurotrophic factor protein induction in the rat hippocampus. Neuroscience 2005; 133(3): 853-61.
[154] Knaepen K, Goekint M, Heyman EM, Meeusen R. Neuroplasticity -exercise-induced response of peripheral brain-derived neurotrophic factor: a systematic review of experimental studies in human subjects. Sports Med. 2010; 40(9): 765-801.
[155] Rojas Vega S, Strüder HK, Vera Wahrmann B, Schmidt A, Bloch W, Hollmann W. Acute BDNF and cortisol response to low intensity exercise and following ramp incremental exercise to exhaustion in humans. Brain Res 2006; 1121(1): 59-65.
[156] Ferris LT, Williams JS, Shen CL. The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. Med Sci Sports Exerc 2007; 39(4): 728-34.
[157] Tang SW, Chu E, Hui T, Helmeste D, Law C. Influence of exercise on serum brain-derived neurotrophic factor concentrations in healthy human subjects. Neurosci Lett 2008; 431(1): 62-5.
[158] Matthews VB, Aström MB, Chan MH, *et al*. Brain-derived neurotrophic factor is produced by skeletal muscle cells in response to contraction and enhances fat oxidation *via* activation of AMP-activated protein kinase. Diabetologia 2009; 52(7): 1409-18.
[159] Rasmussen P, Brassard P, Adser H, *et al*. Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. Exp Physiol 2009; 94(10): 1062-9.
[160] Lewin GR, Carter BD. Neurotrophic Factors. In: rosenthal W, editor. Handbook of Experimental Pharmacology. 220. London: Springer; 2014.
[161] Pan W, Banks WA, Fasold MB, Bluth J, Kastin AJ. Transport of brain-derived neurotrophic factor across the blood-brain barrier. Neuropharmacology 1998; 37(12): 1553-61.
[162] Poduslo JF, Curran GL. Permeability at the blood-brain and blood-nerve barriers of the neurotrophic factors: NGF, CNTF, NT-3, BDNF. Brain Res Mol Brain Res 1996; 36(2): 280-6.
[163] Sharma HS, Cervós-Navarro J, Dey PK. Increased blood-brain barrier permeability following acute short-term swimming exercise in conscious normotensive young rats. Neurosci Res 1991; 10(3): 211-21.
[164] Bailey DM, Evans KA, McEneny J, *et al*. Exercise-induced oxidative-nitrosative stress is associated with impaired dynamic cerebral autoregulation and blood-brain barrier leakage. Exp Physiol 2011; 96(11): 1196-207.
[165] Campos C, Rocha NBF, Lattari E, Paes F, Nardi AE, Machado S. Exercise-induced neuroprotective effects on neurodegenerative diseases: the key role of trophic factors. Exp Rev Neuro Ther 2016; Accepted - In Print.
[166] Stanton R, Happell B. A systematic review of the aerobic exercise program variables for people with schizophrenia. Curr Sports Med Rep 2014; 13(4): 260-6.

[167] Campos C, Mesquita F, Marques A, Trigueiro MJ, Orvalho V, Rocha NBF. Feasibility and acceptability of an exergame intervention for schizophrenia. Psychol Sport Exercise 2015; 15: 50-8.

[168] Leutwyler H, Hubbard EM, Vinogradov S, Dowling GA. Videogames to promote physical activity in older adults with schizophrenia. Games Health J 2012; 1(5): 381-3.

[169] Gross J, Vancampfort D, Stubbs B, Gorczynski P, Soundy A. A narrative synthesis investigating the use and value of social support to promote physical activity among individuals with schizophrenia. Disabil Rehabil 2016; 38(2): 123-50.

[170] Vancampfort D, De Hert M, Skjerven LH, *et al*. International organization of physical therapy in mental health consensus on physical activity within multidisciplinary rehabilitation programmes for minimising cardio-metabolic risk in patients with schizophrenia. Disabil Rehabil 2012; 34(1): 1-12.

[171] Gonzalez-Heydrich J, Bosquet Enlow M, D'Angelo E, *et al*. Early auditory processing evoked potentials (N100) show a continuum of blunting from clinical high risk to psychosis in a pediatric sample. Schizophr Res 2015; 169(1-3): 340-5.