INVITED REVIEW

Exergames: neuroplastic hypothesis about cognitive improvement and biological effects on physical function of institutionalized older persons

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Abstract
Exergames can be considered a dual task because the games are performed by a man-videogame interface, requiring cognitive and motor functions simultaneously. Although the literature has shown improvements of cognitive and physical functions due to exergames, the intrinsic mechanisms involved in these functional changes have still not been elucidated. The aims of the present study were (1) to demonstrate the known biological mechanisms of physical exercise regarding muscle adaptation and establish a relationship with exergames; and (2) to present a neurobiological hypothesis about the neuroplastic effects of exergames on the cognitive function of institutionalized older persons. These hypotheses are discussed.

Key Words: *virtual reality; elderly; nursing-home; physical activity; cognition; neuroplasticity*

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Introduction
Institutionalized older adults tend to have poorer cognitive and physical functions (González-Colaço Harmand et al., 2014; Furtado et al., 2015). Such problems may be associated to decreased cognitive and physical stimulation in long term care institutions (LTCIs). While attempting to offer improved support to older persons, health professionals may limit their independence in performing daily activities. This can exacerbate the disuse cycle of physiological systems, resulting in functional dependence. Therefore some LTCIs have adopted cognitive and physical stimulation programs conducted with older residents. One of the recent interventions adopted is cognitive and motor stimulation using active virtual video games (exergames) (Keogh et al., 2014).

Since 2007, research on exergames (such as Nintendo Wii and XBox Kinect) aimed at promoting health has gradually increased. Several of these applications have emerged with different aims, including investigations about the cardiovascular responses of young adults (Monteiro-Junior et al., 2014), the motor ability of neurological patients (Monteiro Junior and Silva, 2012), postural balance (Jorgensen et al., 2013) and cognitive function of older adults (Maillot et al., 2012), among other themes.

The majority of studies regarding this theme show the effects of this new therapy on physical functions in the elderly. Postural balance is the most studied physical capability related to exergames, while few studies have investigated cognitive function. Both cognitive and physical functions are important for the functional autonomy of older persons.

Exergames can be considered a dual task (Pichierri et al., 2012) because the games are performed by a man-videogame interface, requiring cognitive and motor functions simultaneously. Interaction occurs through accelerometers, strain gauges (Pichierri et al., 2012) or cameras which record the motions performed by gamer and send these signals *via* wireless or infrared to the device. These images are generated and projected on a screen. The interface allows the individual to interact with the virtual environment through his/her body movements, requiring cognitive abilities such as spatiotemporal perception, working memory and executive function (Maillot et al., 2012). The necessity of performing coordinated movement simultaneously with the virtual environment events leads to the individual receiving a load of cognitive and physical stimulus. In their systematic review, Laufer et al. (2014) demonstrated the possibility of increasing postural balance in older persons using exergames. Padala et al. (2012) verified that institutionalized older adults improved their postural balance and gait after this kind of exercise training. Maillot et al. (2012) showed that, in addition to physical function, executive function was also improved in older adults after the exergames training program. Therefore, evidence has been gradually accumulating with regard to the benefits of exergames on cognitive and physical functions of older persons.

Although the literature has shown improvements of cognitive and physical functions due to exergames, the intrinsic mechanisms involved in these functional changes have still not been elucidated and few studies have investigated the biological phenomena of exergames. Therefore, the changes on cognitive and physical functions of older persons submitted to interventions with exergames are still not clear, mainly when considering institutionalized older persons. Moreover, biological mechanisms of exergames on muscle adaptation are still not clarified. In this context, the aims of the present study were (1) to demonstrate the known biological mechanisms of physical exercise regarding muscle adaptation and establish a relationship with exergames; and (2) to present a neurobiological hypothesis about the neuroplastic effects of exergames on the cognitive function of institutionalized older persons. Such a hypothesis is based on the interaction with a virtual environment, which would increase the neural activation in important areas of the brain related to cognitive functions. The neural excitation of the specific circuits related to cognitive functions would increase neural processing capacity, improving sensory interpretation and decreasing response times. Moreover, stimulation of the neural circuits can result in an increase in the synthesis of trophic factors synthesis. Trophic factors are crucial to neuronal survival. These mechanisms can be potentiated by physical exercise, resulting in neurogenesis, synaptogenesis, and angiogenesis. Together, these phenomena can improve cognitive performance and maintain the mental health of institutionalized older persons.

Biological Mechanisms of Physical Exercise and Exergames on Physical Function: What Do We Know?

Exergames can be performed using body weight or additional implements (loads). The majority of exergames requires physical effort, increasing energy expenditure. Peng et al. (2011) showed higher caloric expenditure due to exergames in comparison to rest values. These findings confirm the results of Guderian et al. (2010), that demonstrated that the cardiovascular and metabolic requirements of older adults were higher during training program with exergames. Therefore, the physical effort of exergames may generate important functional adaptations.

Several studies have shown improvements in the physical functions of community-dwelling and institutionalized older people submitted to exergames (Padala et al., 2012; Keogh et al., 2014; Monteiro-Junior et al., 2015). Such findings support the hypothesis on biological adaptations related to this kind of intervention, mainly if we consider the large amount of institutionalized frail older persons. The effort needed to support body weight during the exercises can be considered of moderate to vigorous intensity, since this population shows high declines in physical function. Therefore, a regular training program with exergames for institutionalized older persons can be compared to traditional physical training programs (Padala et al., 2012).

Physical effort proposed by exergames would produce the already known biological mechanisms of traditional physical training. Physical training programs involving multimodal exercises (muscle strength, postural balance, among others) can increase strength and muscle volume, improving functional capacity (Binder et al., 2005; Monteiro-Junior et al., 2015). The changes in muscle fiber can occur due to the mechanical and metabolic stress caused by the physical exercise (Spiering et al., 2008). The tension applied on the muscle fibers could generate certain signaling for cellular adaptations, increasing protein synthesis and decreasing apoptosis (Spiering et al., 2008). Furthermore, the damage on the muscle cells acutely releases interleukin-6 (IL-6), which stimulates the differentiation of the satellite cells into new myonuclei. These myonuclei potentiate protein synthesis, which can result in an increase of muscle tissue volume (Spiering et al., 2008).

The basal level of proinflammatory citokynes is higher in pre-frail and frail older adults than in healthy older adults (Lai et al., 2014). Chronic inflammation is related to sarcopenia, low strength, and low gait speed. In fact, majority of institutionalized older persons are pre-frail or frail. Therefore, the effort needed in exercising with exergames would promote signaling mechanisms such as the Akt-mTOR pathway, increasing muscle strength and hypertrophy, consequently improving the ability to practice daily routine activities. In addition, physical exercise decreases inflammatory and increases anti-inflammatory factors, improving muscle integrity (Walsh et al., 2011). In this sense, research is needed in order investigate exergames effects on inflammatory and anti-inflammatory markers and other muscle cell responses.

In short, physical function is associated to muscle strength increase, which is in turn related to postural balance. These physical qualities are important for the elderly, and could be influenced by exergames (**Figure 1**). Whatever changes occur at a molecular and cellular level, they can be beneficial for older persons with lower fitness levels.

Evidence Supporting the Biological Mechanisms of Exergames on Cognitive Function

In order to perform exergames, the individual should understand and interact with a virtual environment context. Several sensorial informations (visual, auditive, and somato-sensorial) are processed in this interaction. All of these generate a sensorial flow, which may occur through stimuli by tasks with predictable elements (closed tasks) or tasks with random elements (open tasks). Closed tasks requires simple abilities, because they do not suffer environmental variations, while the environment may vary in open tasks, requiring higher attention, inhibitory control, decision making, and speedy reaction times. Executive functions are a fundamental element needed to perform adequate movements in response to an open task stimulus (Taddei et al., 2012). Individuals that participate in physical activities with open tasks show better executive functions and lower reaction times (Taddei et al., 2012). In this sense, the majority of exergames can be considered as open tasks, and may, therefore, improve cognitive functions. Anderson-Hanley et al. (2012) have shown improvements in the executive function of 38 older persons (experimental group) compared to 41 controls. The experimental group performed a training program with a cycle ergometer in the virtual environment (open task) while controls performed the same activity without a virtual reality (closed task). Therefore, exergames can be considered a new perspective regarding interventions to maintain or improve the cognitive functions of older adults, maybe improving some aspects related to quality of life (Keogh et al., 2014).

Virtual reality and its interactivity have an impressive ability to attract the attention of any individual towards the game. In the literature, this is known as gameplay. The virtual environment, game settings, aims, challenges, rules, feedback system, interaction, and immersion are some of the factors that contribute for this attraction. All these factors together can stimulate cognitive and sensorimotor functions and emotions.

The interactions with the virtual environment depend on planning, decision making, inhibitory control, and episodic memory, which allow the player to interpret the stimuli that occur during the displacement into the virtual environment (Maguire et al., 1998). Such cognitive functions are associated to executive functions, which are crucial for the day-to-day of older adults, mainly if these people are institutionalized (González-Colaço Harmand et al., 2014). Therefore, the stimuli offered by virtual reality exercises can increase the functionality of important specific brain circuits linked to cognition. Maguire et al. (1998) demonstrated that the hippocampus, caudate nuclei, frontal and parietal cortex and cerebellum are the main areas that become more active during navigation into the virtual environment. The activation of the hippocampus was related to episodic memories and allocentric navigation, which allow the individual to displace him/herself into the environment using a "topographic map". The increase of inferior parietal cortex activity was related to egocentric displacement (based on the body as the center of spatial orientation), while caudate nuclei activity was related to displacement speed. The authors also demonstrated that left frontal cortex activity was associated with virtual tasks related to changing displacement direction, problem solving, and decision making. Such findings indicate that both cortical and subcortical regions can be stimulated by a virtual environment. Thus, the activation of these regions is important to maintain the independence of older persons, since these structures are involved in both basic and instrumental daily routine activities.

According to the context, the stimulus offered through exergames may trigger neuroplastic phenomena. You et al. (2005) demonstrated that individuals who suffered strokes modified their cortical functional organization to conduct motor tasks. These results occurred after one month of training programs with exergames. It is possible that neuroplastic mechanisms (*e.g.*, neurogenesis, synaptogenesis, and angiogenesis) can occur due to this intervention, since both physical exercise and cognitive stimulation (alone or together) can induce structural and functional changes in the brain (Matta Mello Portugal et al., 2013). Therefore, exergames can be a therapeutic strategy in both the prevention and treatment of cognitive disorders in institutionalized older adults.

Taking into consideration that the dual tasks proposed by exergames requires physical effort, it is possible that trophic factors such as brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF-1), glial cell derived neurotrophic factor (GDNF), basic fibroblast growth factor-2 (FGF-2), and others are synthesized and secreted peripherally during the execution of these activities. These factors could subsequently travel to the brain and stimulate the differentiation and proliferation of neurons (Matta Mello Portugal et al., 2013). In the previous study cited previously (Anderson-Hanley et al., 2012), the executive functions of older persons were improved after an exergame training program. These improvements were associated to plasma BDNF levels. In their pilot study with an animal model, Ding et al. (2011) identified that exercise increased tissue plasminogen activator (tPA) release. tPA can generate an up-regulation of mBDNF (mature BDNF), increasing the activity of tyrosine kinase B (TRKB) receptors. The increase in mBDNF and the activity of its receptors resulted in hippocampus plasticity, identified by the syntheses of certain proteins, related to synapses (synapsin 1), mitosis (mitogen-activated-protein-kinase, MAPK), gene expression (calmodulin kinase II, CaMKII), and by increases in TRKB receptor density. In addition, Nascimento et al. (2015) demonstrated that older persons with mild cognitive impairment submitted to physical exercise showed improved cognitive function associated to increased plasma BDNF. Therefore, basic and clinical research regarding physical exercise and cognitive stimulation show the potential benefits of these activities, mainly when they are performed together. Thus, we believe that exergames are a new strategy to stimulate neuroplasticity and improve cognitive functions (**Figure 2**). Executive function is the main cognitive functions stimulated by exergames due to decision making, mind flexibility, planning and inhibitory control required. However, it is unclear if older institutionalized persons with neurodegenerative diseases may have the same benefits.

Conclusions

Exergames can improve cognitive and physical functions of institutionalized older adults. The interaction between older people and exergames stimulates brain regions related to cognition. Virtual open tasks can increase sensorial flow, improving executive function. These activities can also be associated to trophic factors released during the exercise, resulting in neuroplasticity. In addition, the physical effort resulting from exergames can generate similar known mechanisms of exercise, contributing to the improvement of physical function. In the future, these mechanisms should be investigated to confirm these hypotheses.

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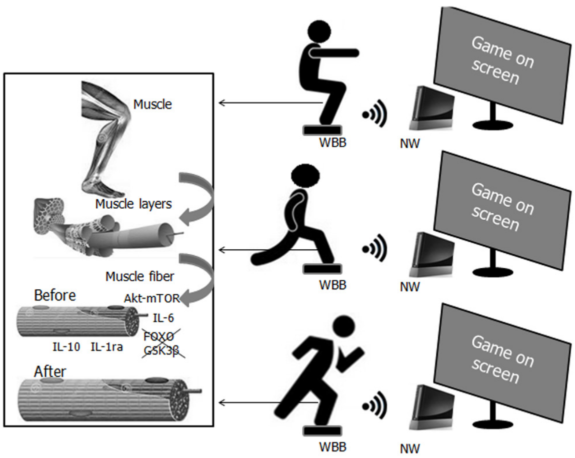

Figure 1 Physical effort during exercise on WBB (a hardware to play). It causes mechanic stress which stimulates Akt-mTOR pathway, IL-6, IL-10, and IL-1ra. Akt-mTOR pathway potentiates protein synthesis, IL-6 increases myonuclei differentiation, and IL-10 and IL-1ra increase chronic anti-inflammatory response. Both signaling result in muscle increased volume. IL: Interleukin; IL-1ra: antagonist receptor of IL-1; WBB: Wii Balance Board; NW: Nintendo Wii.

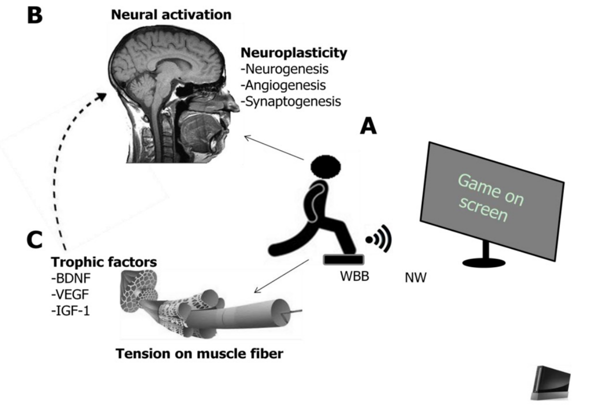

Figure 2 Central and peripheral mechanisms of exergame. (A) An individual playing exergame. (B) Exergame increases neural activation. Long-term neural activation stimulates neuroplasticity. (C) Exergame promotes a muscle fiber tension. Consequently, it increases the synthesis and secretion of trophic factors. Trophic factors traffic by vessels until blood-brain barrier and act on the brain potentiating neuroplasticity (dashed arrow). BDNF: Brain-derived neurotrophic factor; IGF-1: insulin-like growth factor 1; NW: Nintendo Wii; VEGF: vascular endothelial growth factor; WBB: Wii Balance Board (a hardware to play).

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