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Home-based exergames to improve cognitive function in Multiple Sclerosis:

the EXTREMUS Study

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Chapter 1. Multiple Sclerosis

1.1 Epidemiology and pathogenesis

Multiple Sclerosis (MS) is a chronic inflammatory disease affected the Central Nervous System (CNS). MS has a neurodegenerative and immune-mediated character, characterized by a succession of inflammation, multifocal demyelination, gliosis or scarring, a process through which "plaques" form, and neuronal loss. It is the most common demyelinating disease and is second only to trauma as a cause of neurological disability in youth (Noseworthy et al., 2000).

MS is characterized by inflammatory infiltrates to the white substance (WS) and gray substance (GS) located both in brain and in spinal cord. These lesions determine the suffering of the myelin sheath that covers the axon, the extension of the neuronal cell through which it conducts information in a centrifugal direction. Axon demyelination is the underlying cause of MS. Worldwide, there are about 2.5 million people affected by MS, of which 400,000 in Europe and 57,000 in Italy (Cossu et al., 2013).

From the epidemiological point of view is a disease in which the onset is manifested in the age group between 20 and 40 years, with a peak around 30 years; of course, the incidence is also present in childhood, but in small percentage and even turns out to be very rare after fifty years of life. It has a higher prevalence in females than in males with a ratio that has changed between 1950 and 2000 from 2:1 to 3:1 respectively. Although in men there is a lower prevalence, it is important to remember that men with MS usually have a more aggressive form of the disease with worse prognosis and clinical evolution (Kamm et al., 2014).

MS is a disease whose pathogenesis is difficult to describe, considering its multifactorial nature. There are, therefore, several factors that predispose to this disease, among which we can find environmental factors, genetic factors, and stochastic events.

The presence of geographical gradients has been observed in MS: its prevalence increases away from the equator, while in geographical areas with tropical climates, the prevalence is 10-20 times lower. This seems to be due to the close correlation between MS and sun exposure: the exposure of the skin to ultraviolet rays is essential for the synthesis of Vitamin D, and consequently a deficiency of this vitamin increases the risk of MS (Kamm et al., 2014).

Vitamin D has as main and best-known function to ensure the homeostatic maintenance of calcium and phosphorus, thus influencing the mechanism of bone mineralization and musculoskeletal activity. It also acts by influencing the immune system by participating in the activation and differentiation of CD4+ T lymphocytes, in the production of cytokines and in the functional management of Th1 and Th2 lymphocytes, which play a fundamental role in the pathogenesis and treatment of the disease. Prospective studies have confirmed that vitamin D deficiency is associated with an increased risk of developing MS and that in patients with already known disease, a chronic vitamin D deficiency determines an increase in relapses. This correlation could be explained considering the immune-regulatory effects of the vitamin itself (Ascherio et al., 2010; Tizaoui et al., 2015).

Susceptibility to MS is polygenic and each gene contributes, albeit with a relatively low weight, to the total risk. Nevertheless, it is accepted that the genetic component plays a major role in the development of the disease. In fact, this seems to influence for about 35% the risk of developing the disease, with a type of non-Mendelian inheritance with variable penetrance. The demonstration of this has been obtained through studies conducted on homozygotic twins: if one of the twins is affected by MS, the risk for the other rises to 1 in 3. In dizygotic twins this risk drops to 1 in 15, 1 in 25 if there is an affected brother/sister, up to 1 in 50 if one of the parents has MS (O'Gorman et al., 2013).

Disease risk increases with the degree of genetic code sharing with an affected individual, not with sharing of the family microenvironment (Berardelli and Cruccu, 2019).

The Major Histocompatibility Complex (MHC), located on the short arm of chromosome 6, is certainly the most important region of the entire genome in terms

of susceptibility to MS. This locus can explain an increased risk of developing the disease ranging from 17 to 60%. The mapping of the human genome has identified in the MHC class II region the main determinant of the disease since it is involved in the presentation of peptide antigens to T lymphocytes and therefore of their activation and proliferation. This is the high-polymorphism DR2 locus, which contributes to MS risk in an allele-dependent hierarchical manner. The strongest association is the one found with the DRB1*15:01 allele: this, if present in heterozygosity, increases by about 3 times the risk of MS, 9 times in homozygosity (Cree et al., 2010; Kamm et al., 2014)

Most of the genetic variants are responsible for alterations within the immune system, such as the genes responsible to produce the T lymphocyte stimulator molecule, LFA-3 (CD58), the activation of intra and extracellular transmission pathways involving soluble molecules, with the function of regulation and communication of various immune-mediated processes. Among the genes associated with MS, however, there are some responsible for the transcription of proteins considered valid therapeutic targets: for example, the adhesion molecule VCAM1, the natural ligand of VLA-4, an integrin expressed by leukocytes and blocked by Natalizumab; the receptors for Sphingosine 1-phosphate, target of Fingolimod, the first oral therapy on the market for MS.

However, it is essential to understand the role of environmental factors in determining the onset of the disease because, if it is true that the genetic component weighs for about 35% of the risk of developing MS, it is also true that it is a necessary element, but not sufficient, for the manifestation of the same. From this it is clear how important the external environment is, which seems to influence the risk of developing MS in genetically predisposed individuals by at least 60% (Ascherio et al., 2010).

By convention, risk factors could be divided into modifiable and unmodifiable. Regarding modifiable risk factors, the first to be mentioned is cigarette smoking: tar and other substances present in cigarettes are toxic and, penetrating the lungs at high concentrations, could stimulate the immune system in a direct way, through the activation of Toll Like Receptors (TLR). Thus, smoking increases the risk of developing MS by 1.51 times and perhaps, also influences the type of course

(Ramagopalan et al., 2013). In the literature there are data correlating, in Northern Europe and North America, the high consumption of tobacco with the high rate of MS; there are also works showing that about 44% of MS patients are smokers or were smokers before diagnosis (Hedström et al., 2011).

In addition, smoking is also associated with an increased risk of conversion of the relapsing-remitting form to the secondarily progressive form as well as from a clinically isolated syndrome to full-blown MS. The mechanisms of conversion are not yet known, nor how smoking influences the conversion to full-blown MS. About modifiable factors, recent evidence has identified those associated with early disease onset. A higher-than-normal Body Mass Index (BMI) is found more frequently in subjects who develop the disease at a young age (Munger et al., 2013).

To the second category, the unchangeable factors, is characterizing for female gender, age, and Caucasian race. In fact, Caucasian subjects have a higher intrinsic risk for the disease than Africans or Asians, even when they reside in a similar environment (Ramagopalan et al., 2010). Regarding the role of Epstein Barr Virus (EBV), now universally recognized as a risk factor triggering MS, it is classified as a non-modifiable factor, since one cannot protect oneself directly from the virus. The mechanisms of action by which the virus can be involved in the manifestation of the disease are different:

- Direct action of the virus that, crossing the blood-brain barrier, goes to localize in the nerve cell where it remains in a latent state, reactivating itself during immune depressions and causing disease relapse and myelin damage.
- Molecular mimicry in which antigens common to the virus and the myelin basic protein would elicit the production of antibodies that, initially directed against the virus, would subsequently act against the myelin itself. In turn, the degradation products of myelin provoke the formation of self-reactive antibodies against the myelin itself and in this way the process of demyelination would continue in a self-sustaining manner (Salvetti et al., 2009). The risk of developing MS is 15 times higher in individuals who contract this infection in childhood and even 30 times

higher if contracted during adolescence than in uninfected individuals (Berardelli and Cruccu, 2019).

The pathological feature of MS represented by inflammatory demyelination plaques within the CNS. These consist of a wide variety of immunological and pathological features (Wu and Alvarez, 2011). All originate from an inflammatory process in the areas of lesion: inflammation is a mechanism through which the body, by activating the immune system, protects itself from harmful agents. The proper functioning of the immune system is due to the ability of its cells to recognize what is self (i.e., the organism's own) from what is not self (harmful agents). As long as the immune system is able to discriminate self-molecules from non-self-molecules it allows the body to defend itself appropriately, when there is an imbalance in this mechanism and the cells of the immune system no longer have the ability to discriminate, it favors the origin of autoimmune diseases in which even self-molecules are attacked by the cells of the immune system; MS is just one of these diseases.

The inflammatory process occurs through the release of cytokines, which allow the activation of certain cells responsible for the detection and elimination of the external agent: B T-helper 2 lymphocytes and T lymphocytes (cd4+ and cd8+). The cd8+ T lymphocytes have the task of attacking and lysing the target cell, which in the case of MS is the axonal myelin, thus causing the formation of sclerotic plaques (Sobottka et al., 2009). The pathogenesis of plaque formation is initially characterized by the activation of T lymphocytes (cd8+) and monocytes, which can cross the blood-brain barrier, form the inflammatory infiltrate, and attack the myelin causing damage.

The pathogenetic hypothesis is represented by a non-specific immune insult active T lymphocyte, directed against the CNS myelin; these, through the release of inflammatory cytokines (e.g., TNFα, IFNγ) determine the increased expression of adhesion molecules of the family of integrins (V-CAM) on endothelial cells of the blood-brain barrier. Recognition of these molecules and their binding to their counterparts present on lymphocytes-monocytes (I-CAM) result in the release of lytic enzymes that, by cleaving the endothelial tight junctions, determine the characteristic alteration of blood-brain barrier (BEE) permeability with consequent diapedesis of

immune cells, an infiltration that assumes even more importance if we think of the nervous system as an immunologically privileged site.

At the level of the CNS white matter, resident and activated microglial cells act as antigen-presenting cells, inducing the inflammatory reaction against myelin. However, the specific myelin antigen toward which the inflammatory reaction is directed is unknown: many CNS proteins are recognized as antigenic by the immune system (myelin basic protein-MBP, proteolipid protein-PLP, myelin oligodendrocyte-associated protein-MOG, and S-100 protein), but none has been shown to be the specific MS antigen with certainty.

At this point, the cytokine-mediated release of oxygen free radicals (ROS), complement factors and proteolytic enzymes, associated with a cell-mediated toxicity and the production of antibodies directed against myelin by resident B-lymphocytes, determine the damage of myelin with consequent loss of nerve function.

Myelin damage, in addition to causing a loss of trophic support of the axon is responsible for the slowing and sometimes even the block of the impulse conduction at the neuronal level. This alteration of conduction causes functional consequences represented by a real neurological deficit. This is what happens in an initial and acute phase, then there will be the resolution of edema and inflammation associated with attempts to remyelination of the axon concerned, however, are never complete.

Therefore, in this second phase it will be possible to find a recovery of the neurological deficit that will be only partial. In the late stages, however, because of numerous myelin and axonal damage will be present a chronic damage responsible for the establishment of signs and clinical symptoms irreversible (Lopiano and Bergamini, 2020).

Macroscopically, the topography of the lesions thus formed is quite characteristic. Typical sites of the disease include regions adjacent to the lateral ventricles, corpus callosum, subcortical white matter, optic nerves, brainstem, and spinal cord (Berardelli and Cruccu, 2019).

Anatomically, plaques are irregularly shaped and vary in volume from fractions of millimeters to a few centimeters. Plaques can be classified according to their activity: we speak of acute active plaque, when it is characterized by edema and

inflammation; of chronic active plaque, in which there is an initial inflammatory process associated with demyelination; of chronic silent plaque in which there is an intense astrocytic gliosis.

At the structural level, the lesioned area undergoes an alteration is related to demyelination, the process by which initially the myelin swells and then fragments. The debris is then engulfed by phagocytic cells (macrophages and activated microglia cells). Secondary to the demyelination process, a glial reaction occurs, characterized not only by the phagocytic action of activated microglia cells, but also by the alteration of new elements for, it is hypothesized, the attempted myelin regeneration by oligodendrocytes (Lopiano and Bergamini, 2020).

1.2 Disease course

The course of the disease is still difficult if not impossible to predict at the time of diagnosis. However, it has been possible to identify "patterns" of progression that occur more frequently.

MS is always manifested by episodes of disease flare-ups, also called "relapses" or "pousses", which clinically represent the appearance of a new lesion, in which neurological signs or symptoms appear. Secondary to the acute episode, the disease may go into remission, relapse, or progression. By remission we mean a regression of the symptoms and neurological signs that had characterized the acute episode; by relapse, instead, we mean the appearance of new symptoms or signs that last more than 24 hours. A relapse may leave no deficits or create permanent ones. Progression refers to a steady, progressive worsening of symptoms and signs for at least six months (Kamm et al., 2014; Lopiano and Bergamini, 2020). Recently, the classification system proposed by Lublin and Reingold and in effect since 1996 (Lublin et al., 2014) has been revised.

MS forms currently are:

i. *Clinically Isolated Syndrome* (CIS) is an offspring of this 2014 classification: it is recognized as the first clinical event, exhibiting features of inflammatory demyelination that could evolve into MS, or

remain stable. It cannot be defined as MS because it does not meet the criteria for temporal spread (Perrin et al., 2015). There are two types of CIS: monofocal and multifocal. In the former, the person has only a single neurological symptom, caused by a single lesion; in the latter, the person has multiple signs or symptoms simultaneously caused by multiple lesions (Perrin et al., 2015). Subjects with CIS will not necessarily develop multiple sclerosis, but the percentage of patients who develop the disease within 14 years is very high (88%), especially if the CIS turns out to be multifocal.

ii. *Radiological Isolated Syndrome* (RIS) is instead represented by the presence of lesions that can be traced back to those of MS but without clinical evidence of disease (Milo and Miller, 2014). Most of the time these lesions are incidental findings from other diagnostic investigations. RIS is not considered a true form of MS, but patients in this situation should be monitored over time (Perrin et al., 2015).

iii. *Relapsing-Remitting Multiple Sclerosis* (RR-MS). This is the most common form of MS, accounting for 88% of cases at disease onset. RRMS is characterized by the onset of new neurological symptoms or worsening of pre-existing symptoms, with complete recovery and unpredictable course. In periods of clinical remission there is no progression of the disease, although neurological outcomes may recur with fluctuating course, especially during psychophysical stress and sudden changes in temperature6. The relapses occur and reach the acme in a few hours or a few days, with intervals between relapses not constant. Regression of symptoms generally occurs in one to two months; however, the disease is still active even during periods when the patient is in remission (Waubant and Cross, 2014).

iv. *Secondarily Progressive Multiple Sclerosis* (SP-MS). This form is generally diagnosed retrospectively, following a progressive worsening after an initial course of RRMS. Despite numerous studies, the factors but especially the transition point at which RRMS turns into SPMS are still not well understood, as this transition is usually gradual. Approximately 50% of patients with RRMS have a conversion to SPMS within 10 years, furthermore time interval and percentage of conversion from one form to the other are directly proportional (Waubant and Cross, 2014).

v. *Primary Progressive Multiple Sclerosis* (PP-MS). It affects approximately 10-15% of MS patients and is characterized by a progressive worsening of symptoms from the onset16. It differs from PPMS in that disease progression occurs from the onset, with rare moments of stability and almost no improvement. The pivotal treatment for this form is based on symptom control (Waubant and Cross, 2014).

vi. *Progressive Multiple Sclerosis with Relapses* (PR-MS). MS-PR has a progressive course from the onset associated with one or more relapses, with a recovery that can be complete. The difference with RRMS is that between one relapse and another there is no remission of the disease but rather a progression (Milo and Miller, 2014)

In addition to the relapsing-remitting and progressive forms, there are two other clinical variants of MS: *malignant* (Fulminant MS) and *benign*. The first is a rather rare form, in which there is a rapid progression of the disease that can lead to severe disability or death within a few weeks or months of onset; in addition to the CNS, it also attacks the Peripheral Nervous System (PNS) (Faguy, 2016). The second, on the other hand, is considered such if, at least 15 years after onset, it has not resulted in neurological disability, so the patient can be defined as fully autonomous (EDSS score less than or equal to 3).

Negative prognostic factors for all forms of MS include the progressive course and the increased disability achieved at 2 and 5 years after onset. The accumulation of lesions, with the passage of years, is associated with brain atrophy that correlates with the physical disability that characterizes the progressive forms and with cognitive decline. All forms, however, are associated with increasing disability.

1.3 Signs and Symptoms of MS

MS is an extremely heterogeneous pathology in terms of signs and symptoms, both in terms of the neurological systems involved (pyramidal, cerebellar, sensory, truncal, sphincteric, mental, visual and ambulation), and the degree of impairment and severity. The signs and symptoms that occur tend to vary and manifest themselves according to the site of the lesion, and it is therefore possible to find a wide variety of clinical pictures. Some disorders recur more frequently than others because the areas of demyelination have preferential sites.

When the lesions mainly affect the pyramidal bundles, motor symptoms will mainly occur: muscle weakness, more often in the lower limbs; hyperreflexia, characteristic of Babinski's sign and Hoffman's reflex (Berardelli and Cruccu, 2019); spasticity and rigidity, more frequent in the lower limbs, so as to compromise walking and normal activities. These symptoms are present in 40% of cases at the onset of the disease. These symptoms are often not real clinical evidence, but they manifest themselves in an insidious way, as a functional impairment following fatigue. From the motor point of view, symptoms such as hyposthenia, fatigue and spasticity represent the most frequent and evident cause of disability in multiple sclerosis.

Hyposthenia in MS is considered a real decrease in strength that appears in one or more limbs. If it affects the lower limbs, it can result in walking deficits. Fatigue is initially manifested by an early fatigability and not related to the effort; in the evolution of the disease, this deficit tends to progress becoming in many cases invalidating. Spasticity, due to pyramidal lesions, is characterized by hypertonia of muscle structures and is equally disabling; if not treated pharmacologically and from the rehabilitation point of view, it can also lead to ankylosis of the joints and tendon

alterations. In the most severe forms of the disease, spasticity also affects axial structures causing alterations in respiratory mechanics.

Sensory symptoms are present at onset in 20% of cases, and are consequent to lesions of the posterior cords, spine-thalamic pathways, or posterior root entry areas. These are represented by hypoesthesia, i.e., reduction of sensory perception localized or diffused to various body districts; paresthesia, reported as tingling or numbness sensation; dysesthesias, described as electric shocks, burning, burning pain. Sensory disturbances, especially if localized to the trunk and/or limbs, should induce suspicion of a demyelinating lesion at the spinal cord level. It is not uncommon to observe an alteration of deep sensitivity due to the involvement of the posterior cords of the medulla; therefore, hypopallesthesia, particularly of the lower limbs, and positive Romberg sign will be found. To a lesser extent, pain and paroxysmal symptoms are present; Lhermitte's sign belongs to this group of symptoms, which consists of a sudden onset of a shaking sensation along the column and along the limbs following the flexion of the head (Berardelli and Cruccu, 2019).

One of the most suggestive clinical manifestations of MS is included in visual symptoms. They often present as a single onset symptom: Optical Neuritis (ON). When ON occurs, the patient complains of a partial or complete decrease in visual acuity reported as blurring, associated with a severe retrobulbar pain that becomes more severe with eye movements, due to inflammation of the optic nerve. The visual deficit is generally unilateral, may evolve toward complete or partial resolution, but also progress to complete loss of vision. With the execution of the examination of the visual field is noted, generally, an edema of the papilla. In most cases, neuritis is followed by optic atrophy, characterized by pallor of the papilla. A frequent phenomenon in patients with MS is the flare-up of an old symptom in the absence of a relapse of the disease. This phenomenon, called Uhthoff's Phenomenon, is characterized by a transient reduction of visual acuity following exercise or fever; this manifestation is due to a worsening of nerve conduction following an increase in body temperature (Berardelli and Cruccu, 2019).

We speak of cerebellar symptoms when lesions affect the cerebellum and cerebellar peduncles; among which the most frequent are coordination deficits and

ataxia. Ataxia refers to a lack of coordination of voluntary muscle movements that often leads, in patients with MS, to a deficit of balance in standing and, of course, in walking, which presents with an enlarged base. Ataxia may or may not be accompanied by postural tremor, which extends to the trunk and head, and sometimes to the voice, with characteristic cerebellar dysarthria. Recent evidence has shown that cerebellar-onset forms are associated with a more aggressive course of disease (Waubant and Cross, 2014). In advanced forms of the disease, an ataxic-spastic gait may be established due to the simultaneous involvement of the cerebellar and pyramidal systems. Among the most frequent coordination deficits we find dysmetria, which can be evidenced on neurological examination with classic coordination tests, which is the sign of an important impairment and difficult to recover, and adiadochokinesia of the upper limbs, intentional tremor, pendular nystagmus (Berardelli and Cruccu, 2019)

Truncal symptoms are mainly found in the cranial nerves: diplopia, often consequent to a paralysis of the VI cranial nerve, more rarely of the III or IV, which can also be due to an internuclear ophthalmoplegia, which determines a deficit in eye adduction due to damage to the ipsilateral medial longitudinal fasciculus. Other visual disturbances of a truncal nature that may occur are horizontal gaze palsy and nystagmus, which is often associated with cerebellar symptoms and persists over time.The V and VII cranial nerve can be damaged by the disease, manifesting respectively a trigeminal neuralgia and a facial paralysis. In more severe forms of the disease, there may be damage to the bulbar cranial nerves, manifesting as dysphagia, dysphonia, and dysarthria.

Sphincter symptoms are widespread, particularly imperative urination and incontinence. However, they are rarely onset symptoms, and this varies widely by gender and age. However, the symptomatology seems to be caused by bladder dysfunction, benign prostate obstruction, pelvic relaxation, and stress urinary incontinence (Aharony et al., 2017). In advanced stages, sphincter disorders are of mixed type with detrusor dyssynergy. Sexual disorders due to lesions of the spinal centers with erectile deficit in men and anorgasmia or hypo-lubrication in women are also frequent.

Finally, among the behavioral symptoms that most appear during the history of disease, the one that affects more than half of affected individuals is depression, which can be reactive, endogenous, or part of the disease itself, and can affect the overall health status and cognitive abilities (Waubant and Cross, 2014). Cognitive impairment is present in a high percentage of individuals with MS and can manifest itself in different forms depending on the site of the lesion; in most cases there is an alteration in frontal executive functions, such as attention, working memory, speed of information processing, or in long-term memory, computational ability and verbal fluency (Berardelli and Cruccu, 2019).

Since the symptomatology is extremely heterogeneous, in clinical practice there has been a need to define a standardized scale of assessment. In this way, based on the different deficits affecting the various functional systems, it is possible to assign a disability score that allows the monitoring of the disease of each patient over time.

The Expanded Disability Status Scale (EDSS) is the disability scale according to Kurtzke (Kurtzke, 1983a), through which disability scores are assigned to the eight functional systems: pyramidal, cerebellar, brainstem, sensory, sphincter, visual, cerebral, and walking. Each functional system is assigned a score ranging from 0, preserved function, to 5 or 6, impaired function. The overall EDSS score ranges from 0, which corresponds to a normal, nonpathological neurological examination, to 10, which corresponds to death from MS (Lublin et al., 2014). The sum obtained from the individual systems is not a mathematical sum and considers the fundamental role of ambulation, which affects the entire scale. A patient confined to a wheelchair will have an EDSS=7.0 whatever the score assigned to the other systems, because the disability score assigned to a patient who does not ambulate, but is autonomous in postural transitions, is 7, regardless of the other systems.

1.4 Cognitive disorders in MS

Cognitive impairment in MS is complex and multifactorial, and its pathogenesis includes both white matter and gray matter damage (Chiaravalloti and DeLuca, 2008). To date, cognitive impairment is recognized as a common and substantial consequence of MS. It occurs in 40% to 70% of MS patients and has a significant impact on quality of life: patients who are cognitively impaired are more likely to have loss of self-esteem, lower participation in social activities, and higher rates of divorce (Hakim et al., 2000; S. M. Rao et al., 1991). Thus, cognitive deficits impact many aspects of daily life, such as participation in social activities, driving ability, and employment status; they also significantly reduce health-related quality of life (Langdon, 2011). In terms of treatment and disease management, the presence of cognitive deficits in MS patients reduces adherence to drug and rehabilitation therapy (Langdon, 2011).

Classically, the cognitive impairment associated with MS is labeled as a "subcortical dementia," which has already been described in other neurological conditions such as Huntington's Disease or Parkinson's Disease. The clinical presentation differs from cortical dementias such as Alzheimer's due to the lack of aphasia, apraxia, and agnosia. In contrast, subcortical dementias affect the speed of information processing, memory, and executive functions, and bradyphrenia (global slowing of cognitive function) may often be present (Cummings, 1986). It is commonly believed that it is not brain atrophy or cortical lesions that are responsible for the subcortical dementia that occurs in MS patients, but rather lesions in the deep gray matter (basal ganglia and thalamus), brainstem, and cerebellum (Darvesh and Freedman, 1996) . In addition, changes in personality and psychiatric conditions are common, particularly cognitive inflexibility (Stephen M. Rao et al., 1991) and mood disorders such as anxiety, depression, apathy, and irritability (Benedict et al., 2006b) may appear.

Cognitive impairment in MS patients mainly affects the speed of information processing, short- and long-term memory (Benedict et al., 2006b; Stephen M. Rao et al., 1991).

Occasionally, there may be deficits in verbal fluency and executive functions (Chiaravalloti and DeLuca, 2008). MS-related cognitive impairment is detectable at every stage of the disease: in fact, it has been documented in RIS (Amato et al., 2012), CIS, and early-stage RR-MS (Langdon, 2011; Rocca et al., 2015). The frequency of cognitive impairment tends to increase over time and becomes more pronounced in progressive forms (Langdon, 2011; Rocca et al., 2015; Ruano et al., 2017): the presence of cognitive deficits can reach up to 80-90% in the most advanced stages of the disease and in progressive forms (PP-MS and SP-MS) (Ruano et al., 2017). Considering scientific evidence, some papers establish how the main determinants of cognitive impairment are high physical disability in terms of EDSS, and high age of patients, as well as a long duration of the disease (Ruano et al., 2017). In addition, the presence of cognitive impairment is associated with a higher risk of disease progression over time, and a higher rate of conversion from CSI form to full-blown MS (Deloire et al., 2010; Moccia et al., 2016; Zipoli et al., 2010).

Recent studies have found that deficits in social cognition, a neurocognitive domain identified by the fifth revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM V) (American Psychiatric Association, 2013), are important features of cognitive impairment in patients with MS (Cotter et al., 2016).

The mechanisms underlying the onset and progression of cognitive impairment in MS are still unknown. MRI studies have shown that individuals with MS have focal inflammatory lesions that may play a key role in the disruption of neuronal pathways underlying physiological cognitive functioning (Rocca et al., 2015). This has led to the hypothesis that MS-related cognitive impairment results from a "disconnection syndrome," which primarily affects white matter (Dineen et al., 2009; Preziosa et al., 2016). The origin of the deficit appears to be more complex and multifactorial, resulting from a combination of white matter and gray matter lesions (Calabrese et al., 2015).

Studies have been performed to investigate the relationship between gray-substance lesions and cognitive profile in MS patients, leading to the conclusion that there is a relationship between the two (Calabrese et al., 2009; Harrison et al., 2015). Interestingly, however, the mere presence of cortical lesions is not sufficient to explain

the presence of cognitive deficits (Preziosa et al., 2017). Indeed, it seems that active inflammatory lesions play a central role in the process of cognitive impairment (Harrison et al., 2015).

Gadolinium capturing lesions on MRI can cause transient cognitive deficits due to a focal demyelination effect. This proves that the functioning of the neuronal network is not only affected by the "disconnection" effect by white lesions, but also by the more widespread action of immune molecules that are released during inflammation (Di Filippo et al., 2008).

Neurodegeneration plays an important role in the pathogenesis of cognitive disorders: cognitive performance is in fact linked to the presence of diffuse brain atrophy (Bergsland et al., 2016; Calabrese et al., 2009) and atrophy of thalamus (Bhattacharya et al., 2014), putamen (Batista et al., 2012), hippocampus (Planche et al., 2018), cerebellum (Cocozza et al., 2017), corpus callosum (Granberg et al., 2015) and amygdala (Batista et al., 2017).

MS-related cognitive impairment is thus complex and characterized by the presence of diffuse focal lesions, with both white and gray involvement, concomitant with pathological changes occurring in specific cortical and subcortical structures of the CNS (Di Filippo et al., 2018).

Chapter 2. Premorbid Functional reserve in MS

2.1 Cognitive reserve

Cognitive reserve (CR) refers to individual differences in cognitive processes or underlying neural networks that allow some people to recover better than others in the face of brain damage.

Reserve can be roughly classified into passive and active models. Brain reserve (Katzman et al., 1988) is an example of a passive model, in which reserve is derived from brain size or neuronal count. Larger brains can sustain more insults before a clinical deficit emerges, because the unaffected neural substrate is sufficient to support physiological function. This approach to reserve has been codified in the threshold model (Satz, 1993), which revolves around the construct of "brain reserve capacity": the model recognizes that there are individual differences in brain reserve capacity. It also assumes that once brain reserve capacity is depleted, beyond the critical threshold, specific clinical or functional deficits emerge.

Thus, individual differences in brain reserve capacity led to differences in the clinical expression of a particular degree of brain damage.

This type of model assumes that there is some fixed or threshold limit below which functional impairment will occur for everyone. Second, threshold models are essentially quantitative models, that is, they assume that a specific type of brain damage will have the same effect in every person, and that repeated brain damage adds up. Individuals differ only in their overall brain capacity, and brain damage is sufficient or insufficient to deplete brain reserve capacity at a critical level, not accounting for individual differences in how cognitive tasks are processed.

In contrast to passive reserve models, active models such as CR suggest how the brain attempts to cope with brain damage using pre-existing cognitive processes or enlisted compensatory processes (Stern, 2002). Although two patients might have

the same amount of brain reserve capacity, the patient with more CR can tolerate a larger injury than the other before clinical impairment is evident. Thus, an active model does not assume the presence of a fixed or threshold limit, beyond which functional impairment will occur; rather, it focuses on the processes that allow people to sustain brain injury and maintain function (Stern, 2006).

As is well known, there is great variability in cognitive status among patients with MS, even among patients with similar patterns of disease progression (Benedict et al., 2006a; Deloire et al., 2011). This is evidenced in part by the incomplete correlation between lesion load and cognitive function (Benedict et al., 2006a; Deloire et al., 2011). That is, some patients with MS are better able to cope with lesion load without manifesting cognitive deficits. This dissociation between disease burden and cognitive outcome is also common in other neurological diseases, such as Alzheimer's disease (Boyle et al., 2013; Katzman et al., 1988).

The discrepancy between disease burden and cognitive status (i.e., differential cognitive decline) is partially explained by the cognitive reserve hypothesis (Bennett et al., 2012; Stern, 2012), which postulates that enrichment of life experiences protects against cognitive decline in the face of aging and neurological disease, likely because of the increased capacity and efficiency of neural networks (Stern et al., 2005; Sumowski et al., 2010; Sumowski and Leavitt, 2013).

Support for the cognitive reserve hypothesis has come from evidence that older adults with a history of higher educational attainment or job performance (Stern et al., 1994; Valenzuela and Sachdev, 2006) or engagement in cognitively stimulating leisure activities (J et al., 2003; Scarmeas et al., 2001; Wilson et al., 2002) have a reduced risk for dementia.

Literature work has shown that MS patients with higher education (Benedict et al., 2010; Pinter et al., 2014; Da Silva et al., 2015) and higher literacy (Pinter et al., 2014; Sumowski et al., 2014) are protected from disease-related cognitive impairment and memory problems. In addition, they demonstrated that cognitive activities performed in leisure time contribute to the cognitive status of MS patients independently of cognitive enrichment developed over the life course (J. F. Sumowski et al., 2010) and that initiation of such cognitive activities early in adulthood

attenuates the negative effect of disease burden on cognitive status (Sumowski et al., 2013). Benedict and associates have shown that increased intellectual enrichment protects against decline in cognitive efficiency over nearly 5 years (Benedict et al., 2010), whereas there is work showing that cognitive enrichment is protective against decline in cognitive efficiency and memory over 4.5 years (Sumowski et al., 2014).

CR can help identify individuals who are at higher risk for deterioration and progression. It may offer therapeutic opportunities and strategies based on intellectual and individual reserve enhancement.

Amato and collaborators (Amato et al., 2013b) have noted that, because cognitive defects and cortical atrophy have been documented from the earliest stages of MS, including in CIS and RIS (Sumowski et al., 2013), CR may have a protective role operating early in the disease and extending into the intermediate stages, before brain tissue loss occurs. This suggests the presence of a "time window" of opportunity for potential interventions.

2.2 Motor reserve

The concept of motor reserve (MR) is less defined than that of CR, but the same assumption can still be applied, namely that for the same structural damage to the CNS there are different neurological outcomes.

It could be explained by the level of premorbid physical activity, that is, the levels of physical activity before the onset of disease. Premorbid physical activity has been found to be predictive of chronic diseases, such as cardiovascular disease and depression, in the general population (Warburton et al., 2007) and of motor disability in the elderly population (Keysor, 2003; Paterson and Warburton, 2010).

Some studies demonstrating that physical inactivity, common in people with MS (Motl et al., 2005) is related to vascular-type comorbidities (Motl et al., 2011) and disability progression (Marrie et al., 2010), but not considering premorbid physical activity levels.

Regarding the MR in MS, the only study in the literature (Motl et al., 2012a) demonstrated a relationship between a higher level of premorbid physical activity

and a reduced rate of disability progression over 24 months in people with RRMS. Given the prevalence of inactivity in RRMS (Motl et al., 2005), premorbid physical activity may have a protective function against disability progression in a neurological population: it follows that lifestyle may have an impact on disability progression.

Theoretically, premorbid physical activity results in improved physiologic conditioning, such as increased aerobic capacity, muscle strength, or better balance, which in turn slows the rate of disability progression in persons with a chronically active neurological disease (Durstine et al., 2000), including MS (Motl et al., 2010; Motl, 2010).

There may also be a neural component within this theoretical pathway based on the cross-sectional association between physiological conditioning (i.e., aerobic capacity), cerebral white matter integrity, and gray matter volume, in people with MS (Prakash et al., 2010). Aerobic capacity improves neural integrity, such as in aging (Hillman et al., 2008; Sumowski et al., 2010), and is found to be a protective physiological reserve, preventing the progression of disability. This is comparable to the observation of an independent association between leisure activities and cognitive level in MS: premorbid cognitive activities are predictive of cognitive status through a neural mechanism involving synaptic network processing and increased brain efficiency (Stern, 2006).

In conclusion, the work of Motl and colleagues argues that premorbid physical activity independently predicts change in disability status over a 24-month period in 269 people with RRMS: physical activity, probably early in the disease course, could be an important lifestyle factor in slowing the rate of progression over time among people with MS.

2.3 Premorbid functional reserve and rehabilitation in MS

Introduction

Neural plasticity is the intrinsic property of the CNS to adapt to the ever-changing conditions of the environment encountered during development, learning and even injuries, by reorganizing its structure, function, and connections (Cramer et al., 2011). Neural plasticity also represents the substrate by which the damaged brain relearns lost behaviors through rehabilitation in persons with neurological diseases (Kleim, 2011), including MS (Tomassini et al., 2012). There is indeed growing evidence that the accumulation of disability in MS may be not driven by plasticity exhaustion, but rather by pathological disease processes involving critical neural pathways and by disability-related deconditioning (Tomassini et al., 2012). However, the clinical course of MS, as well as the functional recovery after a rehabilitative intervention, is unpredictable and largely heterogeneous even among persons with similar patterns of disease burden. Such mismatch between brain pathology and its clinical expression is known as the clinical-radiological paradox (Barkhof, 2002) that, in turn, draws attention to the concept of functional reserve, i.e., the adaptability of CNS that allows someone to cope better than others with the MS-related damage (Krieger and Sumowski, 2018).

Functional reserve seems to be mainly influenced by premorbid individual's education, intellect, mental stimulation, participation in leisure activities, social engagement, physical activity, and even dietary factors (Sumowski and Leavitt, 2013b). While premorbid physically and intellectually enriching lifestyles have increasingly been recognized as able to mitigate the risk of MS-related disability, factors associated with improved functional recovery through rehabilitation in MS are largely unknown. Based on the postulate that "*functional improvement afterbrain injury is a relearning process*" mediated by neural plasticity (Kleim, 2011), our working hypothesis is that a greater premorbid functional reserve may contribute –at least partially– to improve the rehabilitation outcome in people with MS.

Premorbid personality traits may also predict functional out-comes, as shown in other neurological conditions (Elmståhl et al., 1996; Sela-Kaufman et al., 2013). To

test this hypothesis, we explored whether the outcome of rehabilitation could be predicted by premorbid physical activity, cognitive reserve, and personality traits in two independent samples of persons with MS who underwent rehabilitative intervention aimed to improve balance and sustained attention.

Methods

In this ancillary study, we sought to include all patients previously enrolled in two pilot randomized controlled clinical trials conducted at the Dept. of Neurology and Psychiatry of Sapienza University, Rome, Italy:

(i) Study 1: a 24-week, randomized, crossover pilot study aimed at exploring the effect of exergames delivered by the Nintendo Wii balance board on balance and gait impairment (Prosperini et al., 2013);

(ii) Study 2: an 8-week, randomized, wait-list control pilot study aimed at exploring the effect of videogames on sustained attention and information processing speed (de Giglio et al., 2015).

Both studies showed a significant effect of homebased training, with a medium effect size both on balance (Cohen's f-squared: 0.20) and attention (Cohen's f-squared 0.18). Furthermore, in both study samples, rehabilitation induced structural and functional changes were also detected in brain areas subserving the trained domains through advanced magnetic resonance (MRI) techniques (de Giglio et al., 2016; Prosperini et al., 2014).

In early 2018, all patients identified from the two afore-mentioned pilot studies (de Giglio et al., 2015; Prosperini et al., 2013)underwent the following assessments: premorbid Historical Leisure Activity Questionnaire (HLAQ) (Motl et al., 2012b), Cognitive Reserve Index questionnaire (CRIQ) (Nucci et al., 2012a), and Temperament and Character Inventory (TCI) (Cloninger et al., 1993).

The HLAQ is an interviewer-administered assessment of leisure time physical activities for adults in different periods of life (Motl et al., 2012b). We have exclusively

collected information on leisure time physical activities conducted by participants ≥10 times in the period between 12 and 18 years of age-time period, i.e., prior the diagnosis of MS. Average attendance in weekly hours was calculated for each single activity according to the following formula: number of years participated in activity multiplied by months per year multiplied by 4 weeks per month multiplied by hours per week divided by 52 weeks per year. The final score was obtained by adding the average weekly hours for all reported activities.

The CRIQ is a 20-item semi-structured interview that, in addiction with collecting demographic data, is aimed at collecting data on the following aspects:

(i) education, that refers to both formal and nonformal education and training years;

(ii) working activity, that includes five occupational categories with different degrees of responsibility and cognitive demands, quantifying years spent in each occupation;

(iii) leisure activity, with information regarding free time activities (sporting activities, reading, watching television, attending concerts, etc.).

The total score is calculated by combining the three sub-scores of each section and after adjusting for age.

The TCI is a self-administered 240-item inventory for seven dimensions of personality traits: four temperaments, namely, novelty seeking (NS), harm avoidance (HA), reward dependence (RD), persistence (PS); and three characters, namely, self-directedness (SD), cooperativeness (CO), and self-transcendence (ST) (Cloninger et al., 1993). The TCI is based on a psychobiological model that attempts to explain the underlying causes of individual differences in personality traits, by correlating specific temperaments with neurotransmitters activity. NS refers to exploratory activity in response to novel stimulation, impulsive decision-making, extravagance in approach to reward cues, quick loss often per, and avoidance of frustration. HA refers to excessive worrying, pessimism, shyness, and being fearful, doubtful, and easily fatigued. RD refers to respond markedly to signals of reward, particularly to verbal signals of social approval, social support, and sentiment. PS refers to perseverance

despite fatigue or frustration. SD refers to regulate and adapt behavior to the demands of a situation to achieve personally chosen goals and values. CO refers to the degree to which a person is generally agreeable in their relations with other people as opposed to aggressively self-centered and hostile. ST refers to the expansion of personal boundaries, including, potentially, experiencing spiritual ideas. Participants were given a revised Italian validated version (Fossati et al., 2007).

Outcome definition

For each study, the magnitude of the change in performance in the primary endpoint of the study, measured as the post training value minus the baseline value divided by the baseline value, was estimated.

In addition, the number of patients who achieved a clinically relevant improvement in the primary endpoint after the rehabilitation intervention was estimated:

(i) for postural sway measurements (main endpoint for the Study 1), the minimal detectable change –i.e., the smallest amount of change which does not result from a measurement error– was 31%, according to literature data (Prosperini et al., 2015a);

(ii) for the SDMT (main endpoint for the Study 2), a raw score changes of 4 points or a 10% change is considered clinically meaningful, according to literature data (Strober et al., 2019).

Statistical analysis

Data are presented as count (proportion) for categorical variables and mean (standard deviation) (SD) or median [interval] for continuous variables. The association between sex and the magnitude of performance change (postural sway for Study 1 and SDMT for Study 2) was explored by the Mann-Whitney U test. Spearman rank-order correlations (unadjusted and adjusted by baseline value) were performed to explore relationships between the magnitude of performance change (postural sway for Study 1 and SDMT for Study 2) and age, years of formal education, disease duration, EDSS score, HLAQ score, CRIQ score, and TCI subscores. We also

ran two hierarchical logistic regression analyses (forward stepwise fashion) to ascertain the effects of some independent variables such as sex, age, years of formal education, disease duration, EDSS score (first step), HLAQ score, CRIQ score (second step), and TCI subscores (third step) on the likelihood of achieving a clinically relevant improvement (dependent variable) in postural sway (for Study 1) and SDMT (for Study 2) after the two types of training. In each subsequent step, the regression equation comprised those in-dependent variables reaching specific thresholds of F- and p-values (for inclusion: $F \geq 1 and p \leq 0.05$; for exclusion: $F < 1$ and $p > 0.05$). Both logistic models were adjusted by baseline value of postural sway (Study 1) and SDMT (Study 2). Odds ratios (ORs), their corresponding 95% confidence intervals (CIs), and p values were provided for any significant independent variables associated with a clinically relevant improvement in postural sway (for Study 1) and SDMT (for Study 2) (dependent variables). Lastly, we conducted two sensitivity analyses estimating the magnitude of a hypothetical unmeasured confounder that would be needed to erase the observed association between the dependent and independent variables.

For each model, we plotted the relative odds between a hypothetical unmeasured confounder and the dependent variable (on the x axis) and between a hypothetical unmeasured confounder and the significant predictors (on the y axis), assuming an arbitrary 20% prevalence of a hypothetical unmeasured confounder. Two-tailed p-values less than 0.05 were considered as significant. Given its exploratory nature, no correction for multiple comparisons was applied.

Results

We achieved 94% ascertainment (34/36) for the Study 1 and 74% (26/35) ascertainment for Study 2. There was no difference in baseline characteristics (i.e., at the original study start) of patients who were identified and those who did not (data not shown). Table 1 shows the main baseline characteristics of patients included in this ancillary analysis, as well as the magnitude of score change from baseline and proportion of patients achieving a clinically relevant change after the training period.

We found no association between baseline patients' characteristics (sex, age, disease duration, disability level) and premorbid HLAQ and CRIQ and TCI subscores

in both studies (data not shown), except for an expected association between formal education and CRIQ (Study 1: rho = 0.671, p < 0.001; Study 2: rho = 0.470, p = 0.015).

Table 1. Demographic and clinical features at baseline (i.e., at the beginning of the original pilot study), magnitude of performance change, and proportions achieving a clinically relevant change in the main study endpoints.

Variable	Study 1	Study 2
Baseline		
Sex female:male, *n* (%)	23:11	16:10
Age in years	42.4 (8.3)	47.7 (8.2)
Formal education in years	14.8 (3.5)	13.6 (2.9)
Disease duration in years	16.3 (6.1)	18.5 (8.5)
EDSS score, median	3.5 [1.5–5.0]	3.5 [1.5–6.0]
After the training		
Magnitude of performance change *	15 (28)	18 (19)
Clinically relevant change, *n* (%)	14 (41)	15 (58)

All values are mean (standard deviation), unless indicated otherwise

*postural sway for Study 1 and SDMT for Study 2

Study 1

Larger training effect on balance and gait, estimated as magnitude of performance change from baseline in postural sway, was associated only with higher HLAQ values (rho = 0.375, p = 0.029), but not with demographic and clinical features, CRIQ, or TCI subscores. This finding was confirmed even after controlling for the baseline value of postural sway (rho = 0.385, p = 0.027) (see also Table 2). Fourteen (41%) patients achieved a clinically relevant improvement in postural sway after the training.

The logistic regression model was statistically significant, $\chi 2$ (2) = 10.359, p = 0.006. The model explained 34% (Nagelkerke R2) of the variance and correctly classified 73.5% of cases. Higher HLAQ values (OR = 2.03, p = 0.031) and higher SD

scores (OR = 1.40, p = 0.051) were associated with an increased likelihood of achieving a clinically relevant improvement in postural sway (see also Table 3).

Sensitivity analysis showed that, assuming a 20% prevalence of an hypothetical unmeasured confounder, its association with either the dependent variable or the independent variables should lead to ORs of 5 to 6 or 3 to 4 to erase the predictive value of HLAQ and SD, respectively, on achieving a clinically relevant improvement in postural sway after the training (Fig. 1/A).

Table 2. Spearman rank-order correlations for magnitude of score change after the training; in bold are reported significant p-values

		Study 1		Study 2	
		Unadjusted	Adjusted	Unadjusted	Adjusted
Age	rho	− 0.086	0.042	0.107	0.092
	p	0.628	0.816	0.604	0.663
Formal education	rho	0.110	0.121	− 0.100	− 0.055
	p	0.534	0.501	0.628	− 0.795
Disease duration	rho	0.026	0.024	0.006	− 0.057
	p	0.886	0.896	0.978	0.787
EDSS score	rho	0.062	0.004	− 0.117	− 0.143
	p	0.726	0.980	0.569	0.496
CRIQ	rho	0.187	0.195	**0.408**	**0.406**
	p	0.288	0.277	**0.039**	**0.044**
HLAQ	rho	**0.375**	**0.385**	− 0.116	− 0.089
	p	**0.029**	**0.027**	0.572	0.673
NS	rho	0.030	0.051	− 0.262	− 0.257
	p	0.866	0.779	0.196	0.215
HA	rho	0.006	− 0.038	− 0.099	− 0.090
	p	0.972	0.835	0.631	0.670
RD	rho	− 0.070	− 0.082	− 0.106	− 0.129
	p	0.696	0.649	0.607	0.539
PS	rho	0.080	0.114	0.039	0.021
	p	0.652	0.527	0.849	0.921
SD	rho	0.235	0.241	− 0.030	− 0.065
	p	0.181	0.177	0.883	0.757
CO	rho	0.017	0.174	− 0.145	− 0.168
	p	0.923	0.334	0.481	0.423
ST	rho	0.297	0.254	0.322	0.339
	p	0.088	0.154	0.109	0.098

CO, Cooperation; *CRIq*, Cognitive Reserve Index questionnaire; *EDSS*, Expanded Disability Status Scale; *HA*, Harm Avoidance; *HLAQ*, Historical Leisure Activity Questionnaire; *NS*, Novelty Seeking; *PS*, Persistence; *RD*, Reward Dependence; *SD*, Self-Directedness; *ST*, Self-Transcendence

Table 3. Predictors of achieving a clinically relevant improvement by hierarchical forward stepwise logistic regression models

	Nagelkerke R-squared	Predictor(s)	OR	95% CIs	*p* value
Study 1	0.34	HLAQ	2.03	1.07–3.87	0.031
		SD	1.40	1.00–1.98	0.051
Study 2	0.41	CRIQ	1.27	1.02–1.57	0.033
		HA	0.66	0.42–1.04	0.075

CRIq, Cognitive Reserve Index questionnaire; *HA*, Harm Avoidance; *HLAQ*, Historical Leisure Activity; *SD*, Self-Directedness

Study 2

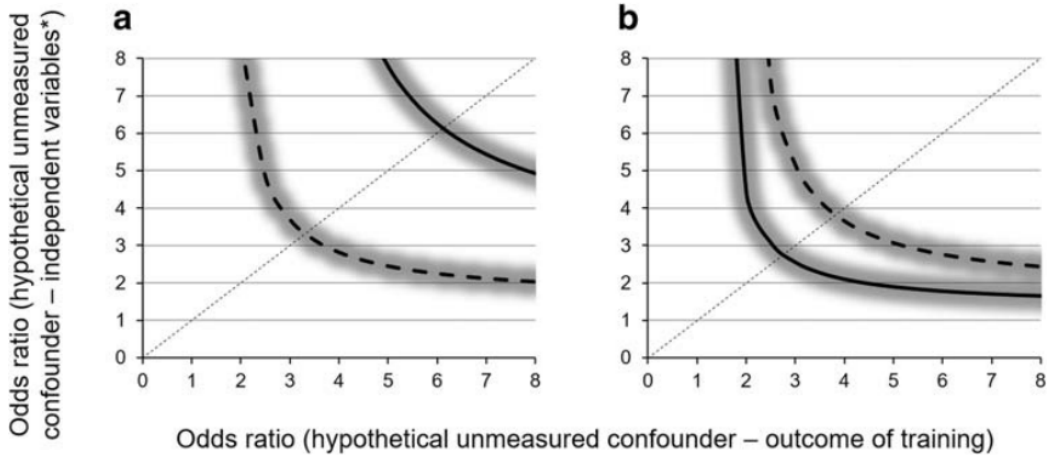
Larger training effect on sustained attention and information processing speed, estimated as magnitude of SDMT performance change from baseline, was associated only with higher CRIQ values (rho = 0.408, p = 0.039), but not with demographic and clinical features, HLAQ, or TCI subscores.

This finding remained unaltered even after controlling for the baseline value of postural sway (rho = 0.406, p = 0.044).

Fifteen (58%) achieved a clinically relevant improvement in SDMT. The logistic regression model was statistically significant, $\chi 2$ (2) = 9.466, p = 0.009. The model explained 41% (Nagelkerke R2) of the variance and correctly classified 76.8% of cases. Higher CRIQ scores (OR = 1.27, p = 0.033) and lower HA scores (OR = 0.66, p = 0.075) were associated with an increased likelihood of achieved a clinically relevant improvement in SDMT (see also Table 3).

Sensitivity analysis showed that, assuming a 20% prevalence of an hypothetical unmeasured confounder, its association with either the dependent or independent variables should lead to ORs of 3 to 3 or 3 to 4 to erase the predictive value of CRIQ and HA, respectively, on achieving a clinically relevant improvement in SDMT after the training (Fig. 1/B).

Fig. 1/A e Figure 1/B.



Sensitivity analyses to define the strength of the association of an hypothetical unmeasured confounder with either the outcome of rehabilitation (dependent variable) and proxies for functional reserves (independent variables) to erase the results of hierarchical logistic regressions predicting the outcome of training to improve balance (A; Study 1) and cognition (B; Study 2).

*A: Historical Leisure Activity Questionnaire (continuous line), and Self-Directedness (dotted line);

B: Cognitive Reserve Index Questionnaire (continuous line), and Harm Avoidance (dotted line).

Discussion

In this study, we tested the hypothesis of an association between improved outcome after rehabilitation and premorbid physical activity, cognitive reserve, and personality traits as proxies for functional reserve. To our knowledge, this issue has so far never been specifically investigated in persons with MS. We found better outcome (i.e., reduced postural sway) after balance rehabilitation as associated with higher level of premorbid physical activities (HLAQ) and SD character (TCI). We also found better outcome (i.e., improved SDMT scores) after rehabilitation of attention as associated with greater cognitive reserve (CRIQ), whereas the HA temperament (TCI) was associated with worse outcome. Our findings suggest an exclusive "intra-modal" modulation rather than a "cross-modal" modulation of rehabilitation outcome by the individual functional reserve, with premorbid physical activity predicting the improvement in the motor domain and premorbid intellectual enrichment predicting the improvement in cognitive domain. While premorbid physically and intellectually enriching lifestyles have increasingly been recognized as able to mitigate the risk of

MS-related disability and brain damage detected at MRI (Motl et al., 2012b; Santangelo et al., 2019; Sela-Kaufman et al., 2013), studies on personality traits in persons with MS are less conclusive.

Some Authors have suggested a possible relationship between personality characteristics and disease stage (Gazioglu et al., 2014), the degree of damage (Fazekas et al., 2013), memory function (Leavitt et al., 2017), and quality of life (Zarbo et al., 2016). Higher values in HA temperament and neuroticism trait were found associated with worse clinical outcomes; however, these findings should be interpreted with caution given that some of these relationships are not confirmed after controlling for depression (Gazioglu et al., 2014) and given that the MS-related cognitive decline may also induce longitudinal personality change (Roy et al., 2018). Consequently, it is not possible to conclude whether the personality trait of persons with MS is a predictor for better or worse outcomes or rather another aspect of the disease-related damage.

Despite of the marked success of disease modifying therapy research, rehabilitation is a key therapy option for many persons with MS, since it promotes the recovery of impaired functions by exploiting neural plasticity (Prosperini et al., 2015b; Tomassini et al., 2012). Nevertheless, factors associated with improved functional recovery through rehabilitation in MS are largely unknown. Studies investigating similar topics in other neurological disabilities provided mixed results. Engagement in premorbid physical activities was proven as a proxy for functional reserve of the motor domain in patients with Parkinson's disease (PD) (Sunwoo et al., 2017) and post-stroke survivors (Yamaguchi et al., 2018), although not confirmed in other studies (Zeliha Karaahmet et al., 2018). Educational attainment is reported to be an independent predictor of better outcomes in traumatic brain injury (TBI) (Schneider et al., 2014) and cerebral small vessel disease (Jokinen et al., 2016).

Longitudinal studies showed a reduced risk of dementia in persons who engaged leisure-time activities and less age-related gray and white matter loss associated with higher levels of physical activity, particularly aerobic exercise (Cheng, 2016). By contrast, other authors found that higher premorbid CRIQ is not associated with a rapid adaptation and recovery from TBI (Steward et al., 2018), and

one study showed even greater improvement in balance associated with lower CRIQ score in patients with PD who underwent a specific rehabilitation program (Piccinini et al., 2018).

We propose at least two (not mutually exclusive) explanations for the discrepancies:

(i) the effect of functional reserve in mediating recovery after CNS damage is only modest, thus suggesting that other key factors, such as the extent of injury and age-related processes, are involved;

(ii) different study designs and methodologies across studies do not allow to draw unequivocal conclusions, thus claiming the need for a framework to investigate this topic (Satz et al., 2011).

Our study should be considered merely hypothesis generating and bears several limitations, mainly due to the small sample sizes and the collection of premorbid proxies for motor reserve, cognitive reserve, and personality traits only after the completion of the interventions (possibly leading to recall bias). While we are confident that this is only a minor concern for HLAQ and CRIQ, we cannot rather exclude that TCI scores may correlate not only with premorbid personality traits but also with disease-induced longitudinal changes (Roy et al., 2018).

Furthermore, we cannot explore if other life periods may have greater effect on functional reserve, therefore failing to provide suggestions on when to promote at maximum physical and/or intellectual activities. Similarly, we cannot confirm whether the promotion of these activities in the early stages of the disease, when the disability level is minimal, can buffer the MS-related disability progression over time, as previously proposed (Sumowski, 2015).

Conclusions

Our study raises the hypothesis that rehabilitation outcome is modulated by premorbid level of physical and intellectual enriched activities, as well as by specific temperament and character traits. These preliminary findings have potentially a twofold implication for future research:

(i) further efforts should be made to better define when and how to promote physical activity and intellectual enrichment in order to strengthen functional reserve;

(ii) assessment of patients' character traits and temperaments may help neurologists to tailor rehabilitation strategies.

The present study was published in Neurological Sciences Volume 41, Issue 5, Pages 1251 – 1257 (including images and tables).

Chapter 3. Exergames and balance rehabilitation in MS

3.1 Balance and postural stability

Balance, or postural stability, is an essential component for carrying out the normal activities of daily life, to carry out both the simplest actions, such as maintaining a correct upright posture or walking while avoiding obstacles, and the most complex and articulated movements, required, for example, during the execution of an athletic gesture.

Balance is the ability to maintain the center of gravity (CoG) within the base of support, with as few oscillations as possible (Nashner and LM, 1989). In physiological conditions, balance is controlled by at least three different systems:

(i) The somatosensory system, comprising the visual, somatosensory, and vestibular systems. The first collects information about the movement and position of the body in space with respect to the objects that surround it; the second is able to record the different sensations of pressure and contraction, and to determine the reciprocal position between different parts of the body and the supporting surface, as well as to integrate information from the surrounding environment; the third has the task of detecting changes in position and speed of the head, thus making it possible to correctly position the eyes, and is particularly important when visual and somatosensory information are inaccurate or unavailable.

(ii) The Neuro-Muscular System. The Nervous System ensures a synergistic and coordinated action of the various muscle groups, which then work in harmony with each other.

(iii) The cognitive system has an important and determining role in the appropriate interpretation of information and in the planning of the

motor response. This system includes various cognitive processes such as attention, memory, and intelligence, which identify feed-forward processes, i.e., provide the ability of anticipation, and adapt actions in response to environmental changes and in the task.

Most body movements occur automatically, once learned: the nervous system can execute movements already known and learning new ones, adapting them to the execution of complex gestures.

Several areas of the encephalon contribute to this activity of movement control and decision: the frontal lobe, the pre-motor cortex, and the motor cortex. While the pre-motor cortex is activated as soon as we think about performing the movement, the motor cortex is activated when the motor gesture is executed.

During the execution of a complex action, planning is necessary: the encephalon, proceeding step by step, will design a movement model that will be verified by the basal nuclei and the cerebellum, and then be executed. It is believed that motor learning in the cerebellum can go to influence, through the cerebello-thalamo-cortical bundles, the primary motor cortex.

The motor system contains mechanisms, called feed-forward mechanisms, which allow for a rapid, harmonious, and anticipatory decision-making attitude with respect to the motor behavior that is about to be performed; the feed-back mechanism, on the other hand, exerts a retroactive control that constantly monitors the entire action. Any changes in movement, therefore, resulting from perturbations can be made by the mechanisms of anticipatory corrections, based on mental representations transduced by the feed-forward mechanism in nerve signals, which through the brainstem and then medullary pathway, reach the peripheral muscle motors.

Posture, both in static and dynamic conditions (i.e., during walking), requires multiple levels of nervous control, since the antigravity action requires a wide and complex coordination. This complexity of action-reaction mechanisms, present in postural management, necessarily requires that all functions related to movement and posture control be distinct but interdependent.

The management of movement execution is at the same time hierarchical and parallel: the hierarchical organization allows the development, in the lower levels, of important reflex mechanisms, thanks to which the higher levels can give only general commands without having to detail the motor act. However, thanks to the parallel mode, the higher levels can interact directly on the lower ones, integrating and vicariate the functions in an immediate way. This aspect is fundamental in the functional recovery of some injuries of the central nervous system.

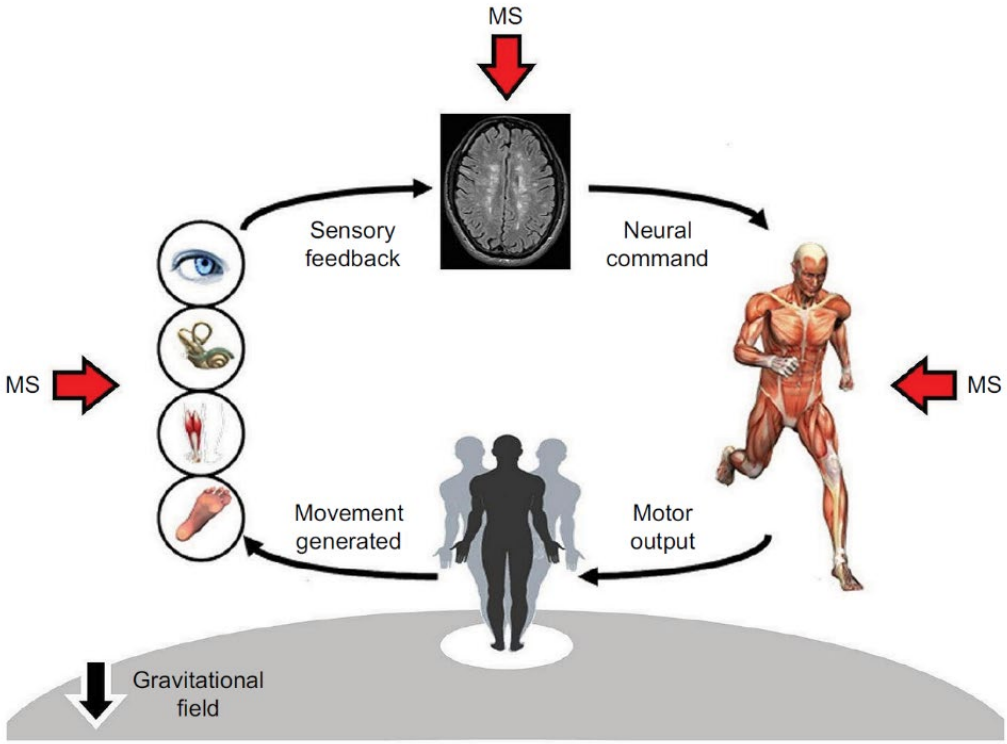
Postural control is developed through the interaction of the perceptual, motor, sensory and cognitive systems, as well as the musculoskeletal system: it is always adjusted before, during and after the execution of each movement, thanks to the constant arrival of information, defining a continuous adaptation to the various situations that arise.

3.2 Balance in MS

Postural control is a structure in which multiple systems are integrated, for this reason it can be influenced by a variety of elements, such as biometric factors, physiological functions, cognitive processing, emotional state, visual feedback, and cerebellar activity. As a result, numerous disorders such as injury, aging, or neurological, otologic, and orthopedic conditions can adversely affect postural sway. Deficiency in any of the mechanisms involved in postural control can produce detrimental effects on balance, causing a sense of instability, vulnerability, as well as predisposing to accidental falls and further injury (Fasano et al., 2012).

MS, by affecting the ability of neurons to communicate efficiently with each other, can also be described as a "disconnection syndrome," and can lead to a variety of neurological and neuropsychological deficits (Dineen et al., 2009). Poor integration of neural pathways, due to the widespread and variable distribution of CNS damage in MS patients, can also affect postural control and the ability to maintain adequate balance (Cameron and Lord, 2010). Postural control may even be compromised by the damage MS causes to peripheral organs that provide sensory input to the CNS or are involved in motor output (Fig. 2).

Fig. 2. Postural control and its alterations in MS.



Very often, altered postural control can be observed in people with MS, and approximately two-thirds of these patients report lack of balance and coordination as the main symptom affecting their mobility in daily life (van Asch, 2011).

Balance impairment reduces mobility and independence, resulting in accidental falls to the ground, injury, and an impact on quality of life (Peterson et al., 2007); in addition, factors such as fatigue, muscle weakness, and spasticity contribute to balance impairment and increased likelihood of accidental falls to the ground (Cameron and Lord, 2010; Finlayson et al., 2006; Giannì et al., 2014; Gunn et al., 2013; Nilsagård et al., 2009).

In fact, overall, the frequency of accidental falls in people with MS is higher than in the general population (Bazelier et al., 2011; Marloes T. Bazelier et al., 2012; M. T. Bazelier et al., 2012; Bhattacharya et al., 2014; Cameron et al., 2011; Ramagopalan et al., 2012). The tendency to fall in these patients may occur early in the course of the disease, even before gait and balance disorders become clinically evident, and even

after the first demyelinating event (Moen et al., 2011). There is work in the literature showing that factors predisposing MS patients to accidental falling to the ground include a progressive form of the disease, a higher level of disability, use of walking aids, worse postural control, and impaired cognition (D'Orio et al., 2012; Giannì et al., 2014; Gunn et al., 2013).

3.3 Gamification and exergames

"Gamification" defines the use of familiar elements of video games in new contexts, which do not include gaming (Deterding et al., 2011; Scholarlycommons et al., 2016). In healthcare, gamification can be used both as health monitoring and to encourage physical activity (Attig and Franke, 2019). For example, some elements of video games used in healthcare include the accumulation of points, levels to achieve, rewards for physical activity performed, and elements of social interaction, such as competitions and challenges with other people (Deterding et al., 2011; Seaborn and Fels, 2015). Often, the purpose of gamification is to mimic gaming experiences to increase player motivation and engagement (Sardi et al., 2017), proving to be a very effective tool.

This type of approach, along with the use of serious games, i.e., games developed solely for entertainment purposes (Deterding et al., 2011; Huotari and Hamari, 2017) are increasingly used in a variety of contexts: health and exercise, (Deterding et al., 2011) education and work productivity (Matallaoui et al., 2017).
The use of game systems for exercise, commonly referred to as exergames, in healthcare settings has seen significant development in recent years (Deterding et al., 2011).

The exergames is based on a technology that provides actions and reactions from the body and detects the movements, thus stimulating not only the eye-hand coordination but the physical exercise of the whole body. Exergames have been shown to be useful in promoting physical activity, counteracting obesity and sedentary behaviors in children and adolescents. Exergames training significantly increases heart rate and energy expenditure, when compared to sedentary, and

results in some improvements even when compared to moderate-intensity physical activities (Peng et al., 2011).

The hypothesis of the effectiveness of exergames is given by the improvement of physical fitness in terms of respiratory capacity, heart rate and energy expenditure. Another hypothesis concerns the recruitment of mirror neurons involved in brain reorganization mechanisms, activated by the presence of an avatar that replicates body movements (Rizzolatti et al., 2009). Observing one's own movements while performing an action facilitates motor learning, even though "the avatar" is not a realistic representation (Cattaneo and Cardini, 2001).

Some elements of exergaming began to be developed as early as the 1980s, but it is only after 2000 that its neurorehabilitation potential began to be glimpsed, thanks in part to the availability and commercial accessibility of platforms such as the Microsoft Kinect, PlayStation Move, and Wii Fit. Currently, their use for neurorehabilitation purposes has been included in the definition of VR-based training and is considered a non-immersive example of virtual reality.

Unlike fully immersive virtual reality, i.e., one that emulates a multisensory living experience in a three-dimensional artificial environment, non-immersive virtual reality involves the use of a smaller scale, two-dimensional environment (such as a TV or personal computer screen, etc.) and interface devices, such as a balance board, motion controllers, or cameras equipped with depth sensors. Some of these devices can also reproduce the sensation of touch through the application of forces, movements, or vibrations.

The use of exergames in neurorehabilitation is efficient, well tolerated, and safe, and not inferior to rehabilitation that does not use video games (Guidi et al., 2013). Due to the presence of elements such as incremental increase in the difficulty of the required task and real-time feedback on fitness and function, in addition to clinical improvement exergames promote learning- and experience-dependent plasticity processes, detected through functional MRI studies, electroencephalography, and increased neurotrophin levels (Golomb et al., 2010).

The use of a rehabilitation protocol with non-immersive virtual reality, in stroke patients, showed activation of the undamaged motor cortex, as well as cerebellar

recruitment and an activation of the compensatory prefrontal cortex (Orihuela-Espina et al., 2013).

Through EEG, improved plasticity of the prefrontal cognitive control system was shown in a group of healthy subjects after one month of home training with a three-dimensional video game in a multi-tasking condition (Anguera et al., 2013).

3.4 Exergames for balance dysfunction in neurological disability: a meta-analysis with meta-regression

Introduction

Falls are a major public health problem worldwide, not only because they represent one of the commonest reasons for unintentional injury death, but also because more than 30 million non-fatal falls require medical care every year (https://www.who.int/news-room/fact-sheets/detail/falls). Together with advanced age, many neurological conditions are associated with an increased risk of accidental falls that contribute to further worsening of neurological disability (Tinetti and Kumar, 2010). Falls occurring in the context of neurological diseases are about twice as frequent as in the general population, especially due to disease-related mechanisms affecting balance and gait (Stolze et al., 2004). This is expected given that the postural control of human balance requires the integration of central and peripheral components that result in complex behaviors based on the interaction of dynamic sensorimotor processes. All the neural components that ensure the correct postural and balance control can be damaged at diferent levels by various neurological diseases (Marshall et al., 2007).

While there is little evidence that pharmacological interventions can improve balance only in a limited number of conditions (e.g., Parkinson's disease (McNeely et al., 2012)), some medications that are largely prescribed in the neurological setting may even worsen balance, especially when multiple drugs are administered (Stolze et al., 2004). Therefore, successful strategies aimed at improving balance and reducing the risk of falls are mainly based on non-pharmacological multidisciplinary interventions, among which stands out the physiotherapy approach (Tinetti and Kumar, 2010). However, common barriers make the access to standard rehabilitation services difficult for all the patients (Chan, 2020). For this reason, alternative interventions that can reach most of the patients, such as video game-based training, can offer an easier, accessible, and possibly more cost-effective approach than standard physiotherapy.

Playing exergames (the portmanteau word for “exercise” and “games”) is a form of whole-body physical exercise delivered by commercial video games (Read and Shortell, 2011a) with the aim of improving fitness and promoting an active lifestyle. The use of commercial devices for neurorehabilitation purposes is considered an example of non-immersive virtual reality based sensorimotor training that can improve balance control and gait (Adamovich et al., 2009). However, accumulating studies investigating the efficacy of exergames on balance have yielded mixed results, possibly due to the heterogeneity of intervention protocols, small sample sizes and low statistical power.

Thus, the effort of integrating and arranging these findings is warranted to estimate more accurately the efects of exergaming on balance dysfunction in neurological conditions. The objectives of this meta-analysis were:

(i) to evaluate systematically the efficacy of exergame-based interventions compared to conventional physiotherapy for balance dysfunction in neurological conditions from randomized clinical trials (RCTs)

(ii) to identify factors of exergaming protocols that may influence their effects.

Methods: search strategy

Our meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Moher et al., 2009) and the review protocol was registered in the PROSPERO database (Registration Number: CRD42020161568). To identify studies to include in this meta-analysis, we searched PubMed/Medline, Scopus, Physiotherapy Evidence Database (PEDro), and Google Scholar, using combinations of free-text and MeSH terms for articles published until December 31, 2019 as follows: ("neurological diseases"[MeSH] OR "nervous system diseases"[MeSH] OR "Neurodevelopmental diseases"[MeSH] OR "multiple sclerosis"[MeSH] OR "Parkins*"[MeSH] OR "Stroke"[MeSH] OR "brain injur*"[MeSH] OR "Trauma"[MeSH] OR "Alzheimer*"[MeSH] OR "Dementia"[MeSH] OR

"intellectual disability"[MeSH] OR"chorea"[MeSH] OR "Cerebral Palsy"[MeSH]) AND ("exergam*"[All Fields] OR "video gam*"[All Fields] OR "Wii"[All Fields] OR "Kinect"[All Fields] OR "Nintendo"[All Fields] OR "Balance board"[All Fields] OR "Computer*"[All Fields] OR "Sony"[All Fields] OR "Dance Dance Revolution"[All Fields] OR EyeToy[All Fields] OR "Microsoft"[All Fields]) AND ("balance"[MeSH] OR "posture"[MeSH] OR "postur*"[MeSH]).

We restricted the search to the following article types: "clinical studies", "clinical trials", "multicenter studies", and "randomized clinical trials". To avoid the risk of missing relevant articles, we searched for additional papers through the bibliography of previous published reviews; we also performed a generic web search.

One reviewing author (LP) ran the search strategy and screened the initial titles after removing duplicates. Two authors (LP and LC) independently examined each potentially relevant article, using the following criteria as defined by the PICO model (O'Sullivan et al., 2013):

(i) population: adult persons (aged ≥18 years) affected by acquired neurological disabilities;

(ii) intervention: "of-the-shelf" exergames (i.e., exergaming-based interventions delivered by commercial devices);

(iii) comparison: conventional treatments or other rehabilitation interventions or no intervention (i.e., waiting-list control group);

(iv) *outcomes*: clinical scales whose area of assessment includes "balance (non-vestibular)" according to the Rehabilitation Measure Database (https://www.sralab.org/rehabilitation-measures). The most frequently reported clinical scale was selected from studies exploring multiple balance outcomes. We decided not to include studies where the balance outcomes were assessed only by instrumented measurements (e.g., static, and dynamic posturography) to limit heterogeneity (Visser et al., 2008).

Additional inclusion criteria were based on study design (parallel or crossover RCTs) and language (articles written in English only). We excluded conference papers, or unpublished materials, as well as articles reporting findings of both non-experimental studies and studies where exergames were delivered by non-commercial video games.

Two authors (LP and LC) independently performed data extraction, with disagreement resolved by a third author (DC). Extracted data included first author name, journal, year of publication, sample size, numbers of men and women, mean age of participants, disease under investigation, eligibility criteria, mean and standard deviation of the outcome of interest, timing of outcome measurement, type of intervention in control group, intervention protocol including type of commercial device, setting (supervised or home-based), administration modality (exclusive or add-on intervention), duration (overall length in weeks), frequency (number of sessions per week) and intensity (minutes spent in a single session) of intervention.

Data on adverse events related with exergames were also collected. If a study had multiple assessments from the same group (e.g., immediate post-intervention and long-term follow-up data), we meta-analysed only the immediate post-intervention data and examined the long-term effect of exergames in a separate analysis. If a study had more than two groups, we meta-analysed only the exergaming group versus the alternative intervention group rather than the no intervention group. When reported data were insufficient for the analysis, we contacted the study author to request access to additional data.

Statistical Analysis

We estimated the pooled effect size of exergame interventions by the bias-corrected Hedges' g with its relative 95% confidence intervals (CIs). This is equivalent to a Cohen's d with an additional correction factor for small samples, thus providing more conservative results. A random-effects model weighted by inverse variance was used to calculate the pooled effect size. Positive effect sizes indicated greater improvement in balance with exergames than alternative interventions.

Effect sizes were graded as small (g=0.20), medium (g=0.50) and large (g=0.80) (Cohen, 1992). To account for the expected heterogeneity between studies and outcome measures of balance, we carried out a random-effects model by entering only post-intervention scores (Chapter 10: Analysing data and undertaking meta-analyses., n.d.). Subgroup analyses were conducted to compare effect sizes between categorical moderators. Meta-regression was run to identify which factors or covariates were associated with a greater effect size of exergames, by using the Hedge's g from each study as dependent variable.

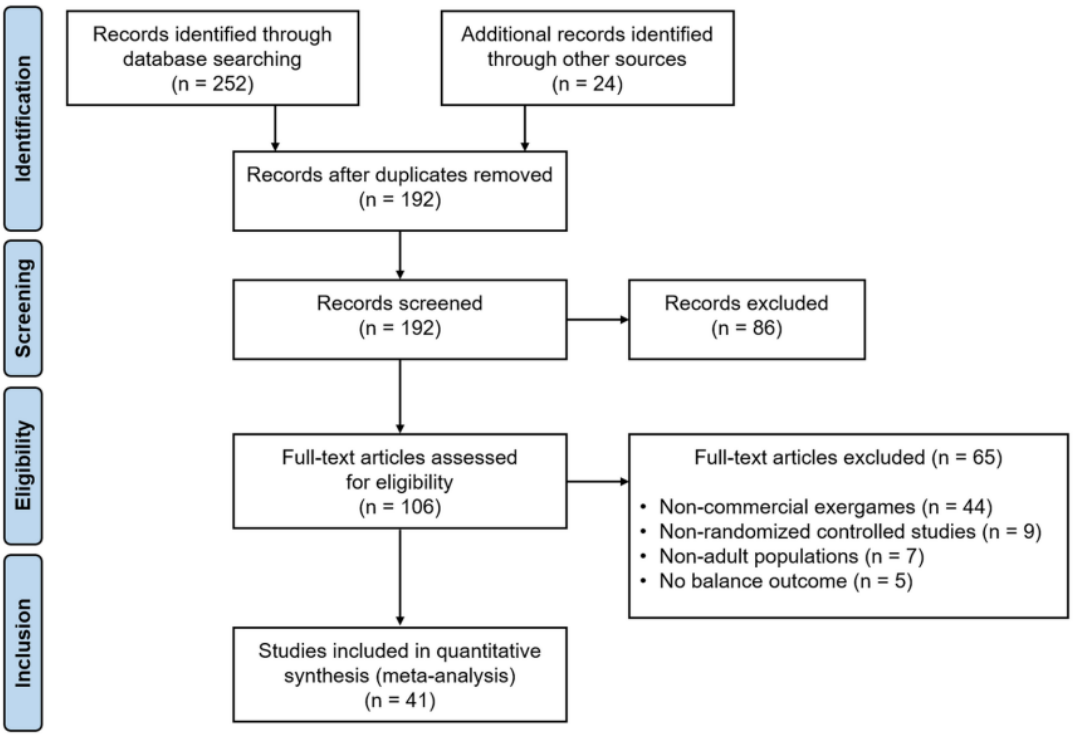
Heterogeneity was assessed by the I^2 index, considering an I^2 ≤40% as marginal, 30–60% moderate and 50–90% substantial heterogeneity, respectively. Risk of publication bias was assessed by visual inspection of funnel plot and the Egger test of asymmetry. We also computed the Orwin fail-safe N test to estimate the number of missing studies that we would need to retrieve and incorporate in our metanalysis to make the summary effect become trivial, on the assumption that studies demonstrating a lack of benefit might not have been published or submitted for publication. Each single study included in this meta-analysis was handled as a statistical unit. Two-tailed p values were considered as significant. Data were analysed by using the OpenMeta(analyst) software.

The methodological quality of each included study was assessed by the PEDro scale (Maher et al., 2003), by downloading the available scores on the website (https://www.pedro.org.au); if a trial had not been rated in the PEDro archive, two authors (LP and AT) independently assessed the rates. Disagreements between authors were resolved by consensus and, if necessary, a third author was consulted (DC). The total score on PEDro scale ranges through the following scores: 9–10 'low' risk of bias; 6–8 'moderate' risk of bias, while RCTs with a score 50% of included studies scored ≤6 on the PEDro scale); inconsistency (significant between-study heterogeneity and I 2≥40%); indirectness (>50% of the participants were outside the target population); imprecision (plot). Consequently, the evidence could be ranked into four levels: very low, low, moderate, and high.

Results

Our initial search of databases retrieved 276 studies, including 24 additional titles that were identified from the bibliography of selected papers and previous published reviews. After removing duplicates and screening from title and abstract, we assessed 106 full-text articles for eligibility. Of these, 41 studies met the eligibility criteria for this metanalysis (Fig. 3) (Arnau et al., 2014; Barcala et al., 2013; Bower et al., 2014; Brichetto et al., 2013; Choi et al., 2018, 2017; Cho et al., 2012; Cuthbert et al., 2014; Fritz et al., 2013; Gandolfi et al., 2017; Gil-Gómez et al., 2011; Golla et al., 2018; Gutiérrez et al., 2013; Hung et al., 2017, 2014; Kannan et al., 2019; Karasu et al., 2018; Lee, 2016; Lee et al., 2017, 2018; Liao et al., 2015; Lozano-Quilis et al., 2014; Morone et al., 2014; Nilsagård et al., 2013; Padala et al., 2017, 2012; Park et al., 2017; Pompeu et al., 2012; Prosperini et al., 2013; Ribas et al., 2017; Santos et al., 2019a; Shih et al., 2016; Song and Park, 2015; Straudi et al., 2017; Tak et al., 2015; Thomas et al., 2017; Tollar et al., 2019; Yang et al., 2015; Yatar and Yildirim, 2015; Yazgan et al., 2020).

Fig. 3. PRISMA flowchart for study selection.



Forty-one eligible studies randomized 1381 participants. Post-intervention data were available for 1223 (88.6%), 621 in the exergaming group and 602 in the control group. Table 4 shows the demographic and clinical characteristics of participants across the included studies.

Table 4. Characteristics of participants in the included studies (n=41)

Study [reference]	Sample size	Men:women ratio	Age	Condition	Clinical scale	Mean baseline score
Barcala (2013) [16]	20	1.2:1	64	Stroke	BBS	38.4
Bower (2014) [17]	21	1.3:1	64	Stroke	TUG	31.1 s
Brichetto (2013) [18]	36	0.6:1	42	MS	BBS	49.1
Cho (2012) [19]	22	0.7:1	64	Stroke	BBS	40.1
Choi (2017) [20]	24	1.4:1	62	Stroke	TUG	15.3 s
Choi (2018) [21]	28	1.5:1	50	Stroke	BBS	48.7
Cuthbert (2014) [22]	20	1.9:1	31	TBI	BBS	47.4
de Oliveira Arnaut (2014) [23]	9	0.5:1	58	MP	BBS	33.4
Fritz (2013) [24]	28	N/A	67	Stroke	BBS	46.6
Gandolfi (2017) [25]	76	2:1	68	PD	BBS	47.1
Gil-Gomez (2011) [26]	17	1.8:1	47	Mixed	BBS	43.3
Golla (2018) [27]	11	1.8:1	74	Stroke	BBS	48.5
Hung (2014) [28]	30	1.8:1	54	Stroke	TUG	27.7 s
Hung (2017) [29]	24	2.4:1	56	Stroke	BBS	48.0
Kannan (2019) [30]	20	1.2:1	59	Stroke	BBS	44.4
Karasu (2018) [31]	23	0.8:1	63	Stroke	BBS	38.9
Lee (2016) [32]	30	1.5:1	64	MCI	BBS	39.8
Lee (2017) [33]	50	2.6:1	57	Stroke	BBS	43.4
Lee (2018) [34]	30	1.5:1	61	Stroke	FRT	8.8 cm
Laio (2014) [35]	24	0.9:1	65	PD	TUG	12.3 s
Lozano-Quilis (2014) [36]	11	1.8:1	45	MS	BBS	49.7
Morone (2014) [37]	47	2.3:1	60	Stroke	BBS	42.1
Nilsagard (2012) [38]	80	0.3:1	50	MS	TUG	11.8 s
Ortiz-Gutierrez (2013) [39]	47	0.7:1	41	MS	BBS	46.0
Padala (2012) [40]	22	0.4:1	80	AD	BBS	42.3
Padala (2017) [41]	30	1.7:1	73	AD	BBS	46.1
Park (2017) [42]	20	1:1	63	Stroke	BBS	36.5
Pompeu (2012) [43]	32	1.1:1	67	PD	BBS	52.4
Prosperini (2013) [44]	36	0.4:1	36	MS	FSST	17.4 s
Ribas (2017) [45]	20	0.7:1	61	PD	BBS	49.6
Santos (2020) [46]	27	2.2:1	64	PD	BBS	42.0
Shih (2016) [47]	20	4:1	68	PD	BBS	50.6
Song (2015) [48]	40	1.2:1	51	Stroke	TUG	18.9 s
Song (2017) [49]	53	0.7:1	66	PD	TUG	9.5 s
Straudi (2017) [50]	21	4.3:1	36	TBI	TUG	16.3 s
Tak (2015) [51]	26	3.3:1	46	MP	FRT	16.7 cm
Thomas (2017) [52]	29	0.1:1	49	MS	TUG	10.9 s
Tollar (2019) [53]	50	N/A	70	PD	BBS	24.2
Yang (2014) [54]	12	3:1	60	Stroke	BBS	12.5
Yatar (2015) [55]	30	1.3:1	63	Stroke	BBS	42.6
Yazgan (2019) [56]	27	0.2:1	43	MS	BBS	44.8

AD Alzheimer's disease, BBS Berg Balance Scale, FRT Functional Reach test, FSST Four-Step Square Test, MCI mild cognitive impairment, MP myelopathy, MS multiple sclerosis, N/A not available, PD Parkinson's Disease, TBI traumatic brain injury, TUG timed up-and-go test

The age distribution and men:women ratio varied according the diseases under investigation, that were stroke (n=17) (Barcala et al., 2013; Bower et al., 2014; Choi et al., 2018; Cho et al., 2012; Fritz et al., 2013; Golla et al., 2018; Hung et al., 2017, 2014; Kannan et al., 2019; Karasu et al., 2018; Lee et al., 2017, 2018; Morone et al., 2014; Park et al., 2017; Song and Park, 2015; Yang et al., 2015; Yatar and Yildirim, 2015), Parkinson's disease (n=8) (Gandolfi et al., 2017; Liao et al., 2015; Pompeu et al., 2012; Ribas et al., 2017; Santos et al., 2019a; Shih et al., 2016; Song et al., 2018; Tollar et al., 2019), multiple sclerosis (n=7) (Brichetto et al., 2013; Gutiérrez et al., 2013; Lozano-Quilis et al., 2014; Nilsagård et al., 2013; Prosperini et al., 2013; Thomas et al., 2017; Yazgan et al., 2020), mild cognitive impairment or early Alzheimer's disease (n=3) (Lee, 2016; Padala et al., 2017, 2012), traumatic brain injury (n=2) (Cuthbert et al., 2014; Straudi et al., 2017), and myelopathy (n=2) including tropical spastic paraparesis (Arnau et al., 2014) and traumatic spinal injuries (Tak et al., 2015); one study included a mixed population of patients affected by stroke, traumatic brain injury, and benign cerebral neoplasm (Gil-Gómez et al., 2011).

The overall disability level of participants was moderate, with almost all the studies requiring adequate visual acuity and hearing function, ability to walk independently or at least to stand upright without assistance. Only one study enrolling patients with severe spinal cord injury required the ability to sit independently (Tak et al., 2015).

Four studies did not report an explicit recruitment criterion for independence in standing or walking (Karasu et al., 2018; Lee, 2016; Song and Park, 2015; Yang et al., 2015).

A severe cognitive impairment was an explicit exclusion criteria in 35 articles, but screening through specific batteries was performed in 24 studies with the Mini-Mental State Examination (n=23) (Choi et al., 2018, 2017; Cho et al., 2012; Gandolfi et al., 2017; Gil-Gómez et al., 2011; Gutiérrez et al., 2013; Hung et al., 2014; Kannan et al., 2019; Lee et al., 2018; Liao et al., 2015; Morone et al., 2014; Padala et al., 2017, 2012; Park et al., 2017; Pompeu et al., 2012; Ribas et al., 2017; Santos et al., 2019a; Shih et al., 2016; Song and Park, 2015; Song et al., 2018; Tollar et al., 2019; Yatar and Yildirim,

2015), Montreal Cognitive Assessment (n = 1) (Lee et al., 2017), and Levels of Cognitive Functioning (n=1) (Straudi et al., 2017).

Most of the studies were designed as parallel-group trials (n=39) (Arnau et al., 2014; Barcala et al., 2013; Bower et al., 2014; Brichetto et al., 2013; Choi et al., 2018, 2017; Cho et al., 2012; Cuthbert et al., 2014; Fritz et al., 2013; Gandolfi et al., 2017; Gil-Gómez et al., 2011; Golla et al., 2018; Gutiérrez et al., 2013; Hung et al., 2017, 2014; Kannan et al., 2019; Karasu et al., 2018; Lee, 2016; Lee et al., 2017, 2018; Liao et al., 2015; Lozano-Quilis et al., 2014; Morone et al., 2014; Nilsagård et al., 2013; Padala et al., 2017, 2012; Park et al., 2017; Pompeu et al., 2012; Ribas et al., 2017; Santos et al., 2019a; Shih et al., 2016; Song and Park, 2015; Song et al., 2018; Straudi et al., 2017; Tak et al., 2015; Tollar et al., 2019; Yang et al., 2015; Yatar and Yildirim, 2015; Yazgan et al., 2020), while a crossover design and a mixed method was adopted in the remaining two studies (Prosperini et al., 2013; Thomas et al., 2017).

Randomization of participants in three groups was made in fve studies also including a no intervention group (n=4) (Choi et al., 2018; Liao et al., 2015; Tollar et al., 2019; Yazgan et al., 2020) and two groups that underwent either balance re-training or non-commercial video games (n=1) (Hung et al., 2017).

The Berg balance scale was the most frequently investigated balance outcome (n=29) (Arnau et al., 2014; Barcala et al., 2013; Brichetto et al., 2013; Choi et al., 2018; Cho et al., 2012; Cuthbert et al., 2014; Fritz et al., 2013; Gandolfi et al., 2017; Gil-Gómez et al., 2011; Golla et al., 2018; Gutiérrez et al., 2013; Hung et al., 2014; Kannan et al., 2019; Karasu et al., 2018; Lee, 2016; Lee et al., 2017; Lozano-Quilis et al., 2014; Morone et al., 2014; Padala et al., 2017, 2012; Park et al., 2017; Pompeu et al., 2012; Ribas et al., 2017; Santos et al., 2019a; Shih et al., 2016; Tollar et al., 2019; Yang et al., 2015; Yatar and Yildirim, 2015; Yazgan et al., 2020), followed by the timed up-and-go test (n=9) (Bower et al., 2014; Choi et al., 2017; Hung et al., 2014; Liao et al., 2015; Nilsagård et al., 2013; Song and Park, 2015; Song et al., 2018; Straudi et al., 2017; Thomas et al., 2017), functional reach test (n=2) (Lee et al., 2018; Tak et al., 2015), and fourstep square test (n=1) (Prosperini et al., 2013). A post-intervention follow-up assessment was planned in 11 studies after a median time of 8 (range 4–24) weeks following the intervention completion (Fritz et al., 2013; Gandolfi et al., 2017; Hung et al., 2017, 2014;

Karasu et al., 2018; Morone et al., 2014; Padala et al., 2017; Pompeu et al., 2012; Prosperini et al., 2013; Ribas et al., 2017; Thomas et al., 2017; Yatar and Yildirim, 2015).

The main characteristics of the interventions are described in Table 5. Exergames were delivered through the Wii Balance Board, Nintendo® (n=32) (Arnau et al., 2014; Barcala et al., 2013; Bower et al., 2014; Brichetto et al., 2013; Choi et al., 2018, 2017; Cho et al., 2012; Cuthbert et al., 2014; Gandolfi et al., 2017; Gil-Gómez et al., 2011; Golla et al., 2018; Hung et al., 2017, 2014; Kannan et al., 2019; Karasu et al., 2018; Lee, 2016; Lee et al., 2018; Liao et al., 2015; Morone et al., 2014; Nilsagård et al., 2013; Padala et al., 2017, 2012; Pompeu et al., 2012; Prosperini et al., 2013; Ribas et al., 2017; Santos et al., 2019a; Shih et al., 2016; Tak et al., 2015; Thomas et al., 2017; Yang et al., 2015; Yatar and Yildirim, 2015; Yazgan et al., 2020), Kinect, Microsoft® (n=7) (Gandolfi et al., 2017; Gutiérrez et al., 2013; Lee et al., 2017; Lozano-Quilis et al., 2014; Park et al., 2017; Song and Park, 2015; Straudi et al., 2017), or Dance Dance Revolution, Sony® (n=1) (Song et al., 2018); a mixed intervention based on Wii Balance Board plus Play Station 2, Sony® was administered in one study (Fritz et al., 2013).

The intervention with exergames was carried out in a supervised outpatient (n=34) (Arnau et al., 2014; Barcala et al., 2013; Bower et al., 2014; Brichetto et al., 2013; Choi et al., 2018, 2017; Cho et al., 2012; Cuthbert et al., 2014; Fritz et al., 2013; Gil-Gómez et al., 2011; Hung et al., 2017, 2014; Kannan et al., 2019; Karasu et al., 2018; Lee, 2016; Lee et al., 2017, 2018; Liao et al., 2015; Lozano-Quilis et al., 2014; Morone et al., 2014; Nilsagård et al., 2013; Padala et al., 2012; Park et al., 2017; Pompeu et al., 2012; Ribas et al., 2017; Santos et al., 2019a; Shih et al., 2016; Song and Park, 2015; Straudi et al., 2017; Tak et al., 2015; Tollar et al., 2019; Yang et al., 2015; Yatar and Yildirim, 2015; Yazgan et al., 2020) or home setting (n=7) (Gandolfi et al., 2017; Golla et al., 2018; Gutiérrez et al., 2013; Padala et al., 2017; Prosperini et al., 2013; Song et al., 2018; Thomas et al., 2017), as exclusive intervention (n=24) (Bower et al., 2014; Brichetto et al., 2013; Fritz et al., 2013; Gandolfi et al., 2017; Gil-Gómez et al., 2011; Golla et al., 2018; Gutiérrez et al., 2013; Hung et al., 2014; Kannan et al., 2019; Liao et al., 2015; Lozano-Quilis et al., 2014; Nilsagård et al., 2013; Padala et al., 2017, 2012; Prosperini et al., 2013; Ribas et al., 2017; Shih et al., 2016; Song and Park, 2015; Song et al., 2018; Straudi et al., 2017; Thomas et al., 2017; Tollar et al., 2019; Yang et al., 2015; Yazgan et

al., 2020) or in addition to other type of rehabilitation (n=17) (Arnau et al., 2014; Barcala et al., 2013; Choi et al., 2018, 2017; Cho et al., 2012; Cuthbert et al., 2014; Hung et al., 2017; Karasu et al., 2018; Lee, 2016; Lee et al., 2017, 2018; Morone et al., 2014; Park et al., 2017; Pompeu et al., 2012; Santos et al., 2019a; Tak et al., 2015; Yatar and Yildirim, 2015).

The control group consisted of standard physical therapy (n=23) (Arnau et al., 2014; Barcala et al., 2013; Brichetto et al., 2013; Choi et al., 2017; Cho et al., 2012; Cuthbert et al., 2014; Fritz et al., 2013; Gil-Gómez et al., 2011; Golla et al., 2018; Gutiérrez et al., 2013; Hung et al., 2014; Kannan et al., 2019; Karasu et al., 2018; Lee et al., 2017, 2018; Liao et al., 2015; Lozano-Quilis et al., 2014; Morone et al., 2014; Park et al., 2017; Pompeu et al., 2012; Ribas et al., 2017; Santos et al., 2019a; Tak et al., 2015), different types of balance training (n=6) (Choi et al., 2018; Gandolfi et al., 2017; Hung et al., 2017; Shih et al., 2016; Straudi et al., 2017; Yatar and Yildirim, 2015; Yazgan et al., 2020), waiting list (n=4) (Nilsagård et al., 2013; Prosperini et al., 2013; Song et al., 2018; Thomas et al., 2017), stationary bicycling (n=2) (Song and Park, 2015; Tollar et al., 2019), alternative types of video games (n=2) (Bower et al., 2014; Hung et al., 2017), walking activity (n=2) (Padala et al., 2017, 2012), mirror visual feedback training (n=1) (Yang et al., 2015) and traditional cognitive rehabilitation (n=1) (Lee, 2016). The median duration of the intervention was 6 (range 3–24) weeks; the median frequency was three (range 1–5) sessions per week; the median intensity was 30 (range 15–90) min.

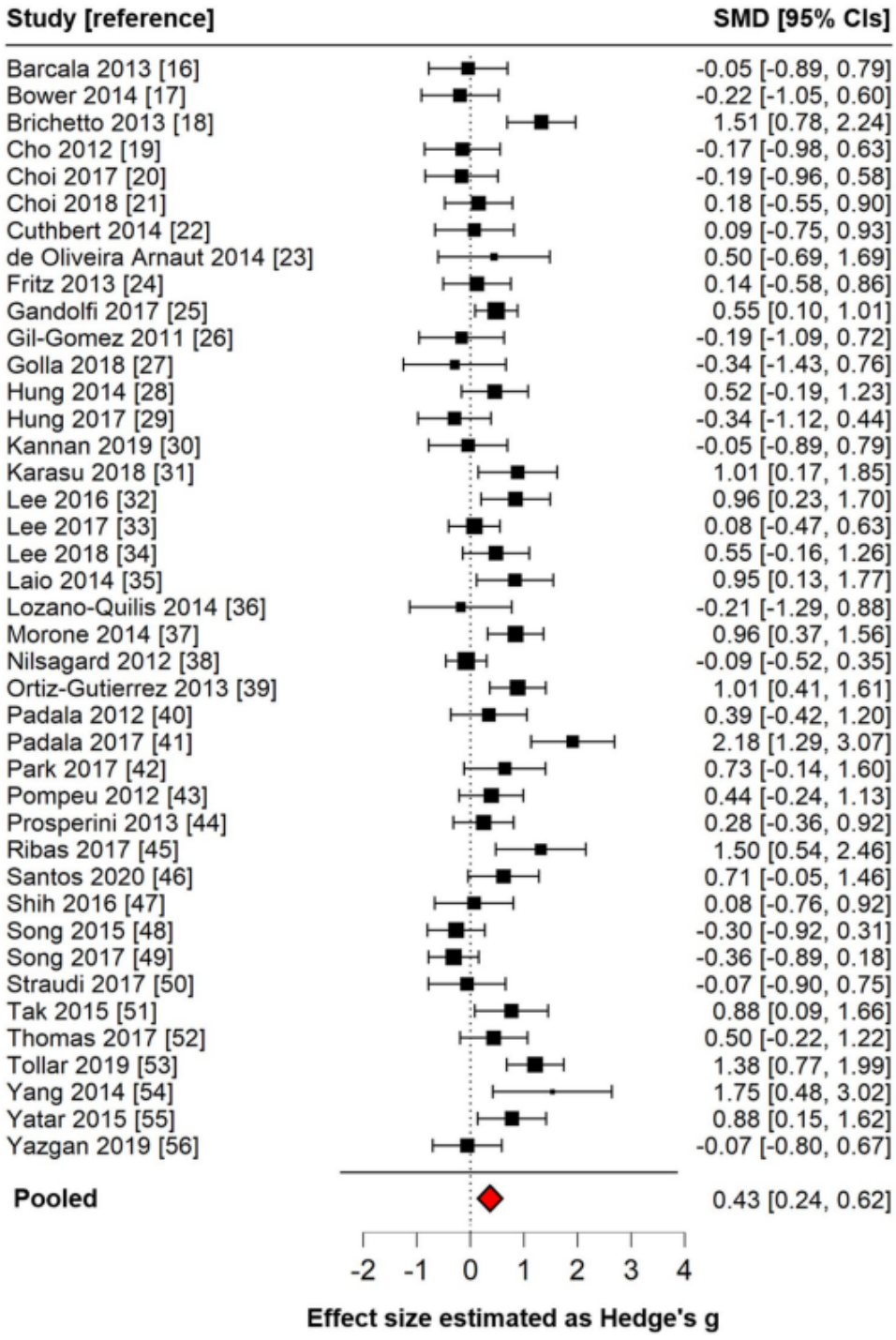
The overall effect size of exergames on balance was moderate (g=0.43; 95% CIs 0.24–0.62, p<0.001), indicating an almost medium effect size favoring exergames over alternative interventions. This finding did not change after removing the four studies where the waiting-list group served as comparator (g=0.48; 95% CIs 0.28–0.67, p<0.001) and after limiting the analysis to studies with Berg balance scale as outcome (g=0.54; 95% CIs 0.31–0.78, p<0.001). Forest plot summarizing the main finding of this metanalysis is shown in Fig. 4.

Table 5. Interventions under investigation in the included studies (n=41)

Study [reference]	Device	Setting	Strategy	Alternative intervention	Duration, weeks	Frequency, sessions per week	Intensity, min per session
Barcala (2013) [16]	Wii-BB	SV	Add-on	Standard physical therapy	5	2	30
Bower (2014) [17]	Wii-BB	SV	Exclusive	Upper limb video games	4	3	45
Brichetto (2013) [18]	Wii-BB	SV	Exclusive	Standard physical therapy	4	3	60
Cho (2012) [19]	Wii-BB	SV	Add-on	Standard physical therapy	6	3	30
Choi (2017) [20]	Wii-BB	SV	Add-on	Standard physical therapy	4	3	30
Choi (2018) [21]	Wii-BB	SV	Add-on	Balance re-training or waiting list	6	3	30
Cuthbert (2014) [22]	Wii-BB	SV	Add-on	Standard physical therapy	4	4	15
de Oliveira Arnaut (2014) [23]	Wii-BB	SV	Add-on	Standard physical therapy	8	2	30
Fritz (2013) [24]	Mixed	SV	Exclusive	Standard physical therapy	5	4	50
Gandolfi (2017) [25]	Wii-BB	HB	Exclusive	Balance re-training	7	3	50
Gil-Gomez (2011) [26]	Wii-BB	SV	Exclusive	Standard physical therapy	5	3	60
Golla (2018) [27]	Wii-BB	HB	Exclusive	Standard physical therapy	6	3	30
Hung (2014) [28]	Wii-BB	SV	Exclusive	Standard physical therapy	12	2	30
Hung (2017) [29]	Wii-BB	SV	Add-on	Balance re-training or non-commercial video games	12	2	30
Kannan (2019) [30]	Wii-BB	SV	Exclusive	Standard physical therapy	6	3	90
Karasu (2018) [31]	Wii-BB	SV	Add-on	Standard physical therapy	4	5	20
Lee (2016) [32]	Wii-BB	SV	Add-on	Cognitive rehabilitation	12	3	40
Lee (2017) [33]	Kinect	SV	Add-on	Standard physical therapy	6	2	90
Lee (2018) [34]	Wii-BB	SV	Add-on	Standard physical therapy	5	3	30
Laio (2014) [35]	Wii-BB	SV	Exclusive	Standard physical therapy or waiting list	6	2	45
Lozano-Quilis (2014) [36]	Kinect	SV	Exclusive	Standard physical therapy	10	1	60
Morone (2014) [37]	Wii-BB	SV	Add-on	Standard physical therapy	4	3	20
Nilsagard (2012) [38]	Wii-BB	SV	Exclusive	Waiting -list	6	2	30
Ortiz-Gutierrez (2013) [39]	Kinect	HB	Exclusive	Standard physical therapy	10	4	20
Padala (2012) [40]	Wii-BB	SV	Exclusive	Walking activity	8	5	30
Padala (2017) [41]	Wii-BB	HB	Exclusive	Walking activity	8	5	30
Park (2017) [42]	Kinect	SV	Add-on	Standard physical therapy	6	5	30
Pompeu (2012) [43]	Wii-BB	SV	Add-on	Standard physical therapy	7	2	30
Prosperini (2013) [44]	Wii-BB	HB	Exclusive	Waiting list	12	4	30
Ribas (2017) [45]	Wii-BB	SV	Exclusive	Standard physical therapy	12	2	30
Santos (2020) [46]	Wii-BB	SV	Add-on	Standard physical therapy	8	2	50
Shih (2016) [47]	Wii-BB	SV	Exclusive	Balance re-training	8	2	30
Song (2015) [48]	Kinect	SV	Exclusive	Stationary bicycling	8	5	30
Song (2017) [49]	DDR	HB	Exclusive	Waiting list	12	3	15
Straudi (2017) [50]	Kinect	SV	Exclusive	Balance platform therapy	6	3	60
Tak (2015) [51]	Wii-BB	SV	Add-on	Standard physical therapy	6	3	30
Thomas (2017) [52]	Wii-BB	HB	Exclusive	Waiting list	24	2	30
Tollar (2019) [53]	Kinect	SV	Exclusive	Stationary bicycling or waiting list	5	5	60
Yang (2014) [54]	Wii-BB	SV	Exclusive	Mirror visual feedback training	3	3	20
Yatar (2015) [55]	Wii-BB	SV	Add-on	Balance re-training	4	3	30
Yazgan (2019) [56]	Wii-BB	SV	Exclusive	Balance re-training or waiting list	8	2	60

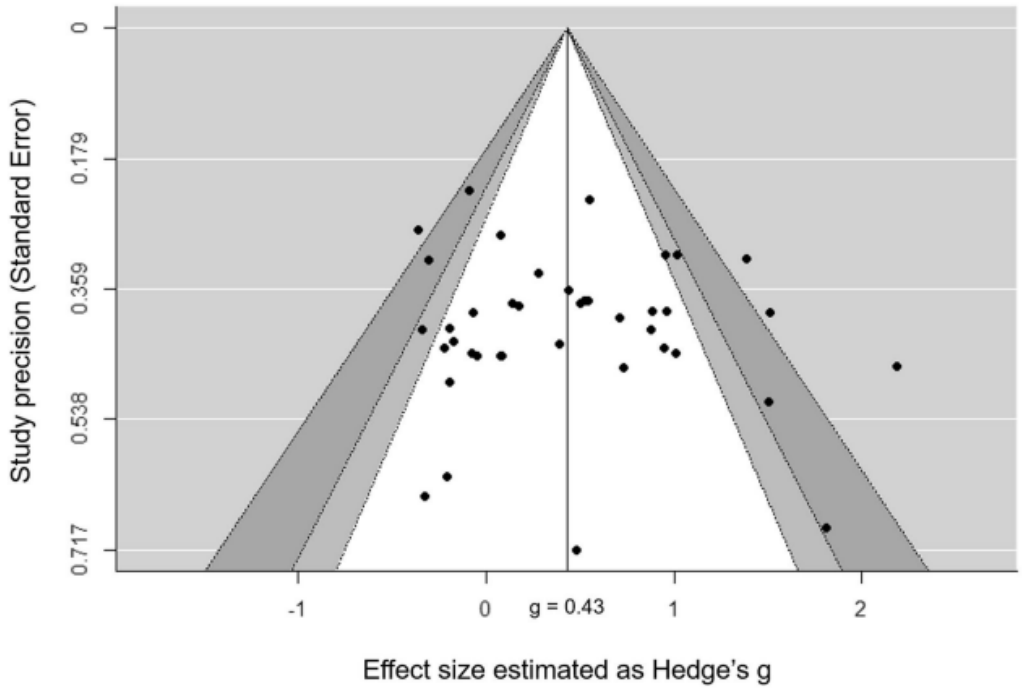
DDR Dance Dance Revolution, *HB* home-based, *SV* supervised, *Wii-BB* Wii balance board

Fig. 4. Forest plot showing the effect size of included studies (n=41) and their pooled effect size (diamond), estimated by an inverse variance random-effects model as standardized mean difference (SMD) and 95% confidence intervals (CI). Positive Hedge's g values indicate a better outcome for exergames.



There was a moderate heterogeneity between the included studies (Q_{40}=97.7, p<0.001, I^2=60%). The Egger test did not reveal significant asymmetry across the included studies (intercept$_{39}$=0.92; t value=0.88; p=0.38), but the visual inspection of funnel plot revealed that three studies overestimated the effect size in favor of exergames and one study overestimated the effect size in favor of the control group (Fig. 5). The Orwin fail-safe N analysis showed that 145 studies with a mean effect size of 0 would be required to alter the significant difference between the exergames and the alternative interventions, i.e., to bring the effect size under a trivial value of <0.1.

Fig. 5. Funnel's plot of included studies (n=41) revealed the existence of publication bias in four studies, in the absence of asymmetry (low risk of reporting bias)



The effect sizes estimated in stroke (g= 0.26; 95% CIs 0.02–0.51, p=0.038), Parkinson's disease (g=0.62; 95% CIs 0.19–0.99, p=0.005), mild cognitive impairment or Alzheimer's disease (g=0.93, 95% CIs 0.37–1.49, p=0.001), and myelopathies (g=0.78, 95% CIs 0.09–1.46, p=0.027) were significant. The effect size estimated in multiple sclerosis (g = 0.44; 95% CIs − 0.03 to 0.91, p =0.065) and traumatic brain injuries (g=0.05, 95% CIs −0.61 to 0.62, p=0.98) were not significant. Exergames delivered through Wii balance board had a significant effect size (g = 0.49; 95% CIs 0.29–0.70, p < 0.001), whereas effect size was not significant with other devices (g = 0.18; 95% CIs − 0.25 to 0.61, p = 0.41). The effect sizes of exergames were significant in both supervised (g = 0.41; 95% CIs 0.21–0.60, p < 0.001) and home-based setting (g = 0.52; 95% CIs 0.01–0.95, p = 0.048), and regardless of being an add-on intervention (g = 0.43; 95% CIs 0.21–0.65, p < 0.001) or not (g = 0.44; 95% CIs 0.15–0.72, p = 0.003).

The effect size of exergames was not influenced by the men:women ratio (β=−0.128, p=0.18) or age of participants (β=0.009, p=0.29), and did not relate to the intensity of a single session (β=−0.003, p=0.56) or to the overall duration of the intervention (β=−0.008, p=0.75). We found a direct relationship between the effect size of exergames and the frequency of weekly sessions, approaching to statistical significance (β=0.16, p=0.057) in the univariate analysis (Fig. 6); this effect became significant in a multivariable analysis including all variables collected for this meta-analysis (β=0.24, p=0.01).

The retention, defined as the consolidation of balance improvement beyond the intervention completion, was investigated in 11 (Fritz et al., 2013; Gandolfi et al., 2017; Hung et al., 2017, 2014; Karasu et al., 2018; Morone et al., 2014; Padala et al., 2017; Pompeu et al., 2012; Prosperini et al., 2013; Ribas et al., 2017; Yatar and Yildirim, 2015) (see also Table 6) where patients were assessed after a median time frame of 8 (range 4–12) weeks following the last session of rehabilitation (henceforth defined as long term assessment).

The effect size of exergames at long-term assessment was moderate (g=0.61, 95% CIs 0.21–0.99, p=0.002) and did not overcome the effect size observed at the immediate post-intervention assessment (g=0.65, 95% CIs 0.35–0.94, p<0.001). The retention effect of exergames appeared to be mediated by the weeks elapsed between

intervention completion and long-term assessment (β = − 0.12, 95% CIs − 0.22 to − 0.03, p = 0.008). However, this indirect association between the retention effect of exergames and the duration of the post-intervention phase became barely not significant after adjusting for the immediate post-intervention effect size (β=−0.07, 95% CIs − 0.16 to 0.01, p=0.08).

Fig. 6. Meta-regression revealed a direct association between the effect size of exergames on balance and frequency of the intervention (number of sessions per week); each circle represents a study, with the circle area proportional to the sample size of that study

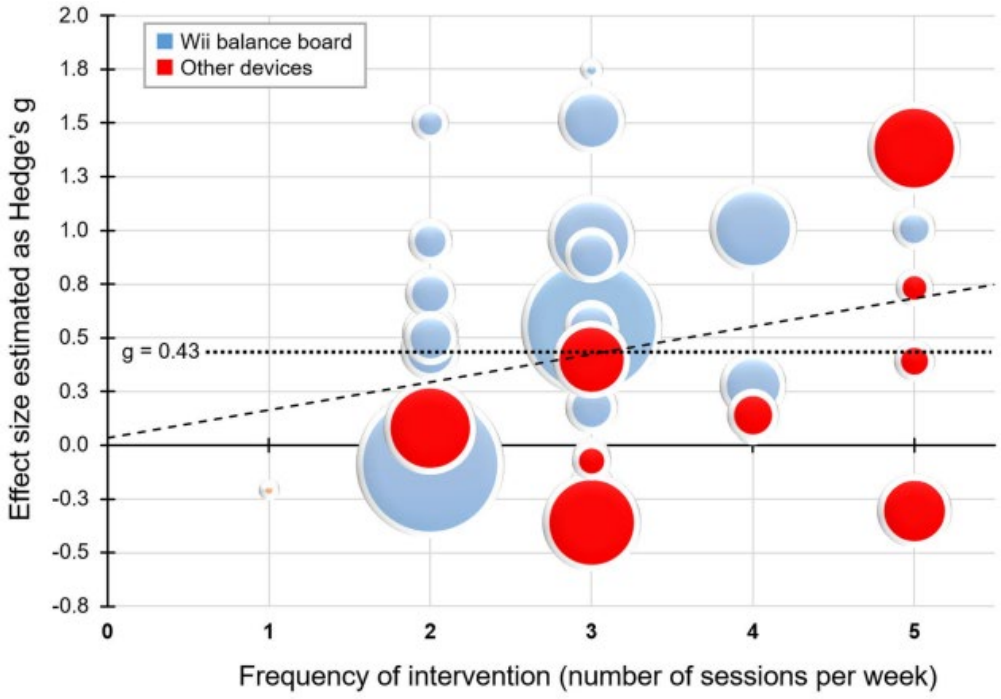


Table 6. Studies investigating the retention effect of exergames on balance (n=11)

Study [references]	Condition	Immediate post-intervention effect size (Hedge's *g*)	Long-term follow-up effect size (Hedge's *g*)	Difference in effect size (%)	Off-intervention duration (weeks)
Gandolfi (2017) [25]	PD	0.55 (0.23)	0.37 (0.36)	−33	4
Karasu (2018) [31]	Stroke	1.01 (0.43)	1.72 (0.30)	70	4
Morone (2014) [37]	Stroke	0.96 (0.30)	1.11 (0.45)	16	4
Yatar (2015) [55]	Stroke	0.88 (0.37)	0.95 (0.23)	8	4
Padala (2017) [41]	AD	1.4 (0.40)	1.67 (0.35)	19	8
Pompeu (2012) [43]	PD	0.44 (0.35)	0.35 (0.33)	−20	8
Ribas (2017) [45]	PD	1.50 (0.49)	0.20 (0.37)	−87	8
Fritz (2013) [24]	Stroke	0.14 (0.37)	0.07 (0.23)	−50	12
Hung (2014) [28]	Stroke	0.52 (0.36)	0.22 (0.40)	−58	12
Hung (2017) [29]	Stroke	−0.23 (0.40)	−0.35 (0.43)	−52	12
Prosperini (2013) [44]	MS	0.28 (0.33)	0.24 (0.49)	−14	12
Pooled effect	–	0.65 (0.15)	0.61 (0.20)	−6	–

AD Alzheimer's disease, *MS* multiple sclerosis, *PD* Parkinson's disease, *SE* standard error

Data on exergaming-related adverse events is available in 22 articles (Bower et al., 2014; Cuthbert et al., 2014; Gandolfi et al., 2017; Gil-Gómez et al., 2011; Hung et al., 2014; Lee et al., 2017; Liao et al., 2015; Lozano-Quilis et al., 2014; Nilsagård et al., 2013; Padala et al., 2017, 2012; Park et al., 2017; Pompeu et al., 2012; Prosperini et al., 2013; Ribas et al., 2017; Santos et al., 2019a; Shih et al., 2016; Song et al., 2018; Thomas et al., 2017; Tollar et al., 2019; Yang et al., 2015; Yazgan et al., 2020), of which 17 reported that no adverse event occurred during the studies. In the remaining six articles, adverse events were always graded as mild or moderate and occurred in 10–38% out of randomized subjects) who reported musculoskeletal disorders (n=5) such as knee, leg, or back pain; accidental falls while playing exergames (n=3); increased spasticity (n=2); dizziness (n=1). There was no serious adverse event reported.

Quality assessment of the included study by the PEDro scale is shown in Table 7. Approximately, 75% of included studies (n=31) were of high quality (rating≥6/10 on the PEDro scale), nine studies were of fair quality (rating 4–5/10 on the PEDro scale), and only one study was of poor quality (rating 3/10 on the PEDro scale). Removing those studies (n=10) of fair or poor quality did not affect the main metanalysis finding (g=0.49, 95% CIs 0.29–0.69, p<0.001).

The most frequent methodological weaknesses of included studies were the lack of double-blindness and the fact that less than 25% of studies reported an

intention-to-treat analysis. The assessment of risk of bias for all included studies is summarized in Fig. 7.

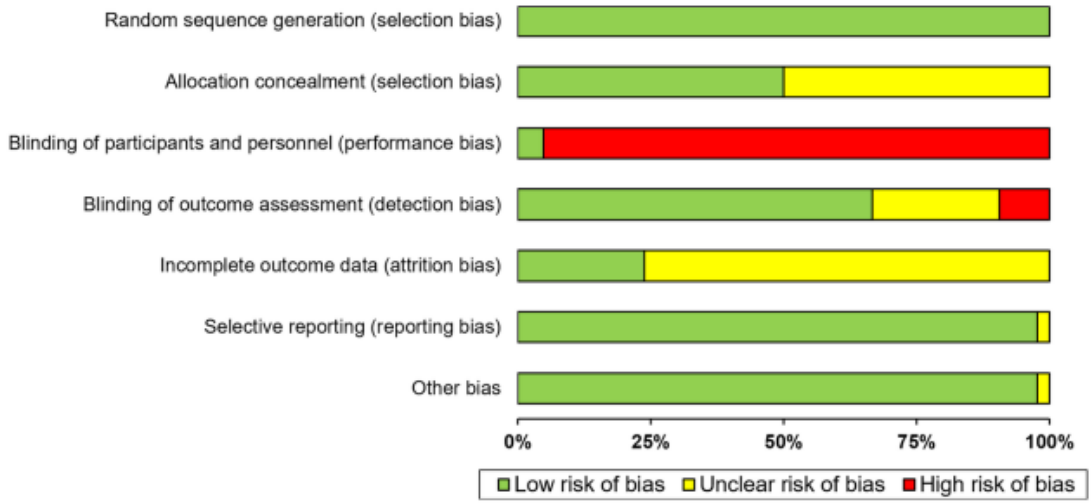
According to the GRADE criteria, an initially assumed high level of evidence was downgraded once, because of the presence of inconsistency due to significant between study heterogeneity and $I^2 \geq 40\%$). Despite inconsistency, our meta-analysis exhibited directness (all participants were affected by balance dysfunction due to neurological diseases), precision (more than 1000 participants) and was free from publication/selection bias across included studies. Consequently, the quality of evidence presented is moderate.

Table 7. Assessment of the methodological quality of individual studies included in the meta-analysis (n=41) by the PEDro scale

Study [references]	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	Score
Barcala (2013) [16]	×	×	×	×			×	×		×	×	7
Bower (2014) [17]	×	×	×	×	×		×	×		×	×	8
Brichetto (2013) [18]	×	×		×			×			×	×	5
Cho (2012) [19]		×		×			×	×		×	×	5
Choi (2017) [20]	×	×		×	×			×	×	×	×	6
Choi (2018) [21]	×	×	×	×			×	×	×	×	×	8
Cuthbert (2014) [22]	×	×		×			×	×		×	×	6
de Oliveira Arnaut (2014) [23]	×	×	×	×						×	×	5
Fritz (2013) [24]	×	×	×	×			×	×	×	×	×	8
Gandolfi (2017) [25]	×	×		×			×	×		×	×	6
Gil-Gomez (2011) [26]		×		×			×	×		×	×	6
Golla (2018) [27]	×	×		×			×	×			×	5
Hung (2014) [28]	×	×	×	×			×	×		×	×	7
Hung (2017) [29]	×	×	×	×			×	×		×	×	7
Kannan (2019) [30]		×		×						×	×	4
Karasu (2018) [31]	×	×	×	×			×	×		×	×	7
Lee (2016) [32]	×	×		×			×	×		×	×	6
Lee (2017) [33]	×	×		×			×	×		×	×	6
Lee (2018) [34]	×	×		×			×	×		×	×	6
Laio (2014) [35]	×	×	×	×			×	×		×	×	7
Lozano-Quilis (2014) [36]	×	×		×				×		×	×	5
Morone (2014) [37]	×	×	×	×			×	×		×	×	7
Nilsagard (2012) [38]	×	×	×	×			×	×		×	×	7
Ortiz-Gutierrez (2013) [39]	×	×	×	×				×		×	×	5
Padala (2012) [40]	×	×		×					×	×	×	5
Padala (2017) [41]	×	×	×	×				×	×	×		6
Park (2017) [42]	×	×	×	×			×			×	×	6
Pompeu (2012) [43]		×		×			×			×	×	5
Prosperini (2013) [44]	×	×	×	×				×		×	×	6
Ribas (2017) [45]	×	×	×	×			×	×		×	×	7
Santos (2020) [46]	×	×		×			×	×	×	×	×	7
Shih (2016) [47]	×	×	×	×				×		×	×	6
Song (2015) [48]	×	×								×	×	3
Song (2017) [49]	×	×	×	×			×	×	×	×	×	8
Straudi (2017) [50]	×	×		×				×		×	×	6
Tak (2015) [51]	×	×		×			×	×	×	×	×	7
Thomas (2017) [52]	×	×	×	×				×	×	×	×	7
Tollar (2019) [53]	×	×		×			×	×		×	×	6
Yang (2014) [54]		×	×	×			×	×		×	×	7
Yatar (2015) [55]	×	×	×					×	×	×	×	6
Yazgan (2019) [56]	×	×		×				×		×	×	5

#1: eligibility criteria (not contributing to total score); #2: random allocation; #3: concealed allocation; #4: baseline comparability; #5: blind subjects; #6: blind therapists; #7: blind assessors; #8: adequate follow-up; #9: intention-to-treat analysis; #10: between-group comparisons; #11: point estimates and variability

Fig. 7. Risk of bias assessment across all included studies (n=41) according to the Cochrane Collaboration



Discussion

In this meta-analysis, we explored to what extent exergaming was superior to physiotherapy or other forms of rehabilitation in improving balance dysfunction due to neurological conditions. We found a significant medium effect size favoring exergames over alternative interventions or waiting list. Further general considerations can be drawn based on the findings of the present meta-analysis.

Firstly, the most robust evidence of a beneficial effect of exergames on balance exists for studies in stroke, Parkinson's disease and, although to a lesser extent, for multiple sclerosis; it is not possible to draw robust conclusions on other conditions, such as mild cognitive impairment or Alzheimer's disease, traumatic brain injuries and myelopathies, mainly due to the smaller numbers of included studies

Secondly, the beneficial effect of exergames on balance was independent of the setting (supervised or home-based) and strategy (exclusive or add-on) of intervention. We observed a between-device difference on effect size, with the Wii balance board-based intervention giving a larger benefit when compared to other commercial devices.

Thirdly, the weekly frequency of sessions, rather than the duration of a single session and the overall duration of the intervention, significantly affected the effect size of exergames on balance. Fourthly, there were some indications of a retention effect of exergames on balance of at least 4 weeks since the intervention completion, suggesting a sustained, but relatively short-lasting consolidation of their beneficial effect, unless exergames are continued over time. However, this latter point should be interpreted with great caution because the retention effect was influenced also by the magnitude of the effect size estimated in the immediate post-intervention phase.

Lastly, exergaming appears to be safe, with only mild to moderate musculoskeletal adverse events reported in a minority of patients, with no significant increased risk of falls (Jalink et al., 2014).

Our fundings are consistent with previously published metanalyses and systematic reviews supporting the efficacy of exergames in the neurological setting (Cano Porras et al., 2018; Goble et al., 2014; Ravenek et al., 2016; Taylor and Griffin, 2015). Meta-analyses investigating the effect of exergames for improving balance

already exist, but they are either focused on specific neurological diseases (Booth et al., 2014; Casuso-Holgado et al., 2018; Laver et al., 2015; Santos et al., 2019b) or incorporate commercial exergames into the wider category of virtual reality-based interventions (Booth et al., 2014; Cano Porras et al., 2018).

To our best knowledge, this is the first attempt to establish what is the optimal use of commercial exergames, in terms of device, setting, strategy, intensity, frequency and duration, to obtain the larger effect on balance. We choose to include only commercial exergames to explore if the lowest cost and easiest accessible solution can be encompassed in the therapeutic armamentarium for the management of balance problems due to neurological conditions. Although this approach cannot replace physiotherapy, based on our findings, we suggest that exergames promote fitness and healthy behavior in patients with mild to moderate disability (i.e., home-based training adaptable to work and family) and can be used to carry over, in the medium term, the effects of physiotherapy in the community setting (i.e., in case of pre-planned or unexpected interruption of rehabilitation). This latter indication comes from the indication of a maintained beneficial effect on balance of at least 4 weeks from exergaming discontinuation, a suggestion that encourages the adoption of a rehabilitation strategy based on "pulsed" exergaming cycles.

Exergames are not free from criticisms for several reasons:

(i) given their commercial nature, game devices have roughly a 5-year life cycle before being replaced with novel hardware, implying that some types of exergames may be no longer available when their application in neurological setting is determined;

(ii) the possibility of a tailored balance re-training is very limited, thereby representing a "blockbuster" rather than a "personalized" intervention (Casuso-Holgado et al., 2018; van Diest et al., 2016; Forsberg et al., 2015);

(iii) being originally designed as a recreational activity, their applicability for the recovery of sensorimotor function is still debated and

consequently the development of custom written game software has been advocated (Forsberg et al., 2015).

The improvement of balance control observed through exergames can result from three (not mutually exclusive) mechanisms: (i) muscle reinforcement; (ii) re-training of sensorimotor strategies aimed to restore the axial control and anticipatory postural adjustments; (iii) engagement of mirror neuron system mediated by the avatar (i.e. the graphical representation of the user in the virtual environment).

Like other forms of bodily exercise, playing exergames increases heart rate, oxygen consumption and energy expenditure to the same extent as a moderate-intensity physical activity (Peng et al., 2011). However, the presumed mechanisms of action of exergames go beyond the merely increase in fitness. By requiring simultaneous physical and cognitive effort, exergames promote muscle reinforcement, as well as increasing efficiency of executive and attentional brain networks. As an intervention, exergaming encompasses most of the principles underlying experience-dependent neural plasticity (Kleim and Jones, 2008), such as high-intensity repetition of task-oriented exercises, incrementally increase of task difficulty, real-time feedback, salience, motivation, and reward. It is worth noting that the frequency of sessions, rather than intensity and overall duration, was associated with larger effect size.

This finding suggests that higher frequency of exergaming may affect consolidation of motor memories through the influence of in-between sessions sleep on synaptic plasticity (Kolb and Muhammad, 2014; Raven et al., 2018). Exergames applied to recovery of balance dysfunction have been also associated with structural and functional brain changes in cerebellar areas subserving postural control and in vestibular cortical network implicated in high-order multimodal integration and cognitive functions, including peri-personal space and self-referential processing (Karim et al., 2012; Prosperini et al., 2014). Their exploitation of complex brain networks makes them also potentially relevant tools to access cognitive domains of otherwise difficult accessibility that are subserved by the same neural circuits or hubs (O'Reilly et al., 2010). A multicenter RCT is ongoing to test the hypothesis that

exergames (delivered by the Wii balance board) are not inferior to cognitive rehabilitation (delivered by a custom-written software application for mobile devices and tablets) and that both interventions are superior to a placebo-analogue cognitive intervention in improving cognitive function and reducing cognitive–motor interference due to multiple sclerosis (ClinicalTrials.gov Identifer: NCT04169750).

Conclusion

Despite the clinical and statistical heterogeneity of included RCTs, our findings provide moderate evidence supporting the use of high-frequency commercial exergames delivered by Wii balance board as either supervised or unsupervised (namely home-based) rehabilitation tool, in addition or not with other interventions, to improve balance dysfunction due to neurological diseases. While the evidence is robust for stroke survivors and people with Parkinson's disease, future investigation is needed to extend recommendation to other neurological conditions and to better determine how long the beneficial effect of exergames lasts after their discontinuation.

The present study was published in Journal of Neurology Volume 268, Issue 6, Pages 3223 – 3237 (including figures and tables).

Chapter 4. Home-based EXergames To impRove cognitivE function in MS

Introduction

Cognitive impairment is common in people with MS, frequently involving domains such as information processing speed, episodic memory, sustained attention, concentration, and aspects of executive functions (Chiaravalloti and DeLuca, 2008; Sumowski, 2015). Cognitive dysfunction can affect patients at any stage of the disease, from radiologically isolated syndrome to later phases of MS (Granberg et al., 2013; Rovaris et al., 2009).

There is no effective pharmacological treatment to manage cognitive impairment in MS (Amato et al., 2013a). Therefore, rehabilitation remains the only strategy to limit the impact of this dysfunction on quality of life. Encouraging results have been reported with computer-assisted training specifically focused on information processing, attention, and executive functions and performed with dedicated software (Goverover et al., 2018). Unfortunately, the time and costs of these cognitive rehabilitative programs limit their applicability in the real life.

To increase the complexity of MS management, very often people with MS have coexisting cognitive and motor deficits and require both cognitive and motor rehabilitation. Therefore, providing a single rehabilitative strategy that can address cognitive and motor issues remains highly desirable.

Exergaming (i.e., playing exergames) is a form of whole-body physical exercise performed through active video games. Research with exergames has focused mainly on promotion of physical activity in the general population and in a variety of neurological cohorts, including MS (Taylor and Griffin, 2015).

In people with MS, exergames have been reported to be safe in-home setting (Prosperini et al., 2013), as well as effective in improving balance, walking speed, muscle strength, dual-task performance, quality of life, fitness level and adherence to

exercise (Brichetto et al., 2013; Forsberg et al., 2015; Kramer et al., 2014; Nilsagård et al., 2012; Pau et al., 2015). Using advanced magnetic resonance imaging (MRI), enhanced brain structural plasticity has been described after 12-weeks of home-based intervention with the Wii balance board (Prosperini et al., 2014). As an intervention, exergaming encompasses most of the principles underlying experience-dependent neural plasticity (Kleim and Jones, 2008), such as high-intensity repetition of task-oriented exercises, incrementally increase of task difficulty, real-time feedback, salience, motivation, and reward, and even transfer effect (Barnett and Ceci, 2002).

Therefore, it has the potential of offering an integrated and adaptable training to improve functions across a variety of domains, from motor to cognitive with interference solving, planning, reasoning, working memory and multi-tasking skills (Levin, 2011). Evidence in the general population and in older adults suggests that action video games can transfer their beneficial effects from motor to cognitive skills (Bavelier and Green, 2016; Bediou et al., 2018).

Meta-analyses of studies on action video gaming effects in healthy subjects and clinically impaired populations reveal small to medium effect sizes on a series of cognitive skills (Mura et al., 2018; Stanmore et al., 2017). However, when considering only patients with neurological disabilities, exergames are equally effective for global cognitive functions and attention, and more effective for executive functions and visuo-spatial perception, compared with conventional therapies.

Despite the afore mentioned meta-analyses, there are only few studies investigating the effect of exergames on cognitive function in MS (Kramer et al., 2014; Prosperini et al., 2013) and none that was designed to specifically test the hypothesis of using exergaming to improve cognitive function in MS. Aim of the study is test the hypotheses that:

(i) exergames and adaptive COGNI-TRAcK (Tacchino et al., 2015) are more effective than sham adaptive COGNI-TRAcK;

(ii) exergames are not inferior to adaptive COGNI-TRAcK.

Methods

This is a phase II, 16-week, randomized, sham-controlled, single-blind, parallel group, multicenter study to test the hypothesis that home-based exergames is not inferior to home-based cognitive rehabilitation delivered by a software application (app) for mobile devices and both interventions are superior to a placebo-analogue intervention in improving cognitive function and reducing cognitive-motor interference in people with MS.

The choice of an 8-week study duration was based on previously published papers on cognitive training delivered by COGNI-TRAcK. In this study, 8 weeks of adaptive COGNI-TRAcK training were sufficient to determine a significant improvement in the SDMT score when compared with sham COGNI-TRAcK, yielding to a post-training between-arm difference of 8 points ($p<0.001$) (Pedullà et al., 2016). The 8-week post-training follow-up period will allow us to investigate the retention of training effect, which is an underinvestigated topic in MS rehabilitation setting. Literature data provide conflicting results (no retention for exergames, 6-month retention for cognitive rehabilitation) (Pedullà et al., 2016; Prosperini et al., 2013).

To participate, patients had to meet the following inclusion criteria: (i) age between 18 and 65 years (inclusive); (ii) cognitive impairment, defined as failure in the SDMT, defined as a corrected score less than 38, i.e., below the 5th percentile of normative value (Amato et al., 2006); (iii) EDSS score between 2.0 and 6.5 (Kurtzke, 1983); (iv) ability to stand upright for at least 180 seconds without any support; (v) ability to understand and comply with study requirements; (vi) ability to provide a valid informed consent before any study procedure.

Thus, those patients who had the following criteria were excluded: (i) relapse in the previous 6 months; (ii) initiation of disease-modifying or symptomatic treatments or physiotherapy program in the 3 months prior to study entry; (iii) any medication/physiotherapy changes occurring over the previous 3 months; (iv) significant visual impairment, defined as a Visual System scoring more than 2 at the Kurtzke Functional Systems Score (Kurtzke, 1983); (v) clinically relevant depression, defined as Beck Depression Inventory-II (BDI-II) score equal or more than 14 (Solaro

et al., 2016); (vi) overt dementia, defined as an adjusted Mini Mental State Examination (MMSE) score equal or less than 24 (Folstein et al., 1975); (vii) history of epilepsy or seizures; (vii) any medical condition, including musculoskeletal disorders that can interfere with the study conduction.

Study assessment

MS patients eligible for the study were randomized in a 1:1:1 ratio to exergames or adaptive COGNI-TRAcK or sham COGNI-TRAcK. The three groups performed three different types of home training:

(i) active video games of balance delivered by the Wii balance board, from here onwards called 'exergames' (intervention of interest);

(ii) Cognitive Training Kit (COGNI-TRAcK) with increasing difficulty levels, from here onwards called 'adaptive COGNI-TRAcK' (comparator intervention);

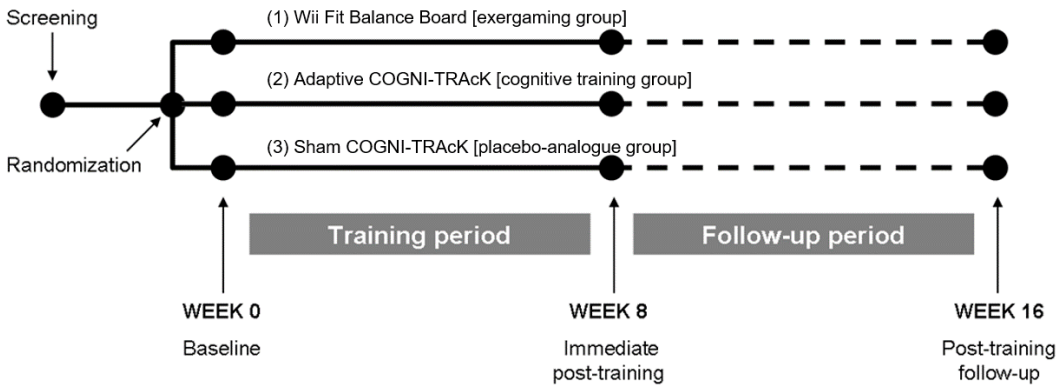
(iii) COGNI-TRAcK at constant difficulty level, from here onwards called 'sham COGNI-TRAcK' (placebo-analogue intervention) (Pedullà et al., 2016).

Randomization codes were computer generated in blocks of six to ensure an approximate 1:1:1 balance among the three arms. Blinding was ensured by use of the single-blind technique. A two-operator model (treating and evaluating) was used to help mask the study. Patients who were screened for enrollment but were not randomized (eg, because they did not meet eligibility criteria or did not provide valid informational consent) were considered as screening failure and their data were not analyzed.

This study includes two periods (training period and follow-up period) and three visits (Fig. 8):

- on Week 0, at study enrolment/randomization (baseline visit);
- on Week 8 (+/- 5 days), i.e. after the end of the 8-week training period (Week 8 visit);
- on Week 16 (+/-5 days), i.e. at study termination after the 8-week post-training follow-up period (Week 16 visit).

Fig.8. Study design



Only at the baseline visit (week 0) was the patient's eligibility confirmed (screening for clinically relevant depression and manifest dementia by administration of the BDI-II and MMSE, respectively), and a neurological examination with EDSS score was done.

The Temperament and Character Inventory (TCI), Cognitive reserve index questionnaire (CRIq), and Historical Leisure Activities Questionnaire (HLAQ) were administered at baseline to explore whether individuals' personality dimensions and pre-morbid motor and cognitive reserve can predict motivation and adherence to the intervention, as well as the magnitude of its effects, according to the postulate that

individual differences in cognitive processes or neural networks allow some people to cope better with brain injury.

The TCI is a 240-item self-report inventory that provides scores describing four temperaments, namely Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RD), Persistence (P); and three characters, namely Self-Directedness (SD), Cooperativeness (C), Self-Transcendence (ST). The TCI is based on a psychobiological model that attempts to explain the underlying causes of individual differences in personality traits (Cloninger et al., 1993). Patients with MS exhibited higher harm avoidance and lower self-directedness scores than the general population, although these differences disappeared after controlling for depression (Gazioglu et al., 2014). In this study, we used a reduced 56-item version developed by Adan and colleagues (Adan et al., 2009).

The CRIq is an interviewer-administered questionnaire which includes some demographic data (date and place of birth, gender, place of residence, nationality, marital status) and 20 items grouped into three sections, education, working activity, and leisure time, each of which returns a subscore (Nucci et al., 2012b). Higher CRIq scores seems to have a protective role in preserving cognitive functions, moderating the effect of MS-related structural damage on cognitive performance (Rocca et al., 2019).

The HLAQ is an interviewer-administered assessment of leisure time physical activity during discrete life periods (e.g., 12–18, 19–34, 35–49, and =50 years of age) (Kriska et al., 1988). We only will include data from the life periods before the confirmed diagnosis of MS. Higher HLAQ scores seems to be associated with slower MS-related disability progression (Motl et al., 2012b).

At the baseline visit (week 0), at the end of the intervention period (week 8 visit), and at the end of the study (week 16 visit), patients were assessed with the Brief International Cognitive Assessment for MS (BICAMS) and the Stroop Color Word Test (SCWT), the 29-item Multiple Sclerosis Impact Scale (MSIS-29) and the 21-item Modified Fatigue Impact Scale (MFIS-21). In addition, they were assessed with the 2-Minute Walking Test (2MWT), the Timed Up&Go test (TUG) and a static posturography under single and dual task conditions.

BICAMS was recently developed as a brief, practical, and universal assessment tool for cognitive impairment in MS; it includes tests of mental processing speed, Symbol Digit Modalities Test (SDMT), verbal memory, the California Verbal Learning Test-2 (CVLT2), and visuo-spatial memory, the Brief Visuospatial Memory Test-Revised (BVMT-R) (Langdon et al., 2012). BICAMS is recommended by an expert consensus committee of neurologists and neuropsychologists as a brief, practical and universal assessment tool for cognitive impairment in MS. The battery takes 15 minutes to complete, requires no specialist equipment and no specialist expertise in cognitive assessment.

SDMT represents a simple screening test for cognitive impairment (Parmenter et al., 2007; Sepulcre et al., 2006). An improvement of 4 points or 10% in magnitude is considered clinically relevant (Benedict et al., 2017). To test some aspects of executive function not explored by the BICAMS, the Stroop Color-Word Test (SCWT) is also included in the assessment (Barbarotto et al., 1998). SDMT presents a series of nine symbols, each of which is paired with a single digit, labelled 1 to 9, in a key at the top of a sheet. The remainder of the page has a pseudo-randomized sequence of the symbols, and the subject must respond with the digit associated with each of these as quickly as possible. The score is the number of correct answers in 90 seconds. The SDMT scores will corrected by educational level as recommended elsewhere (Amato et al., 2006).

The SCWT is also included since the BICAMS does not assess some aspects of executive function. The SCWT evaluates the ability to elaborate relevant and irrelevant dimensions in parallel and to inhibit an automatic response while performing a task based on conflicting stimuli. The procedure comprised of three trials: (i) read a list of words indicating colours printed in black ink as quickly as possible; (ii) name the colour of strings of dots as quickly as possible; (iii) name the colour of the ink of words indicating conflicting colours as quickly as possible (interference condition) (Barbarotto et al., 1998). The practice effect associated with multiple assessment was minimized in two ways: (i) multiple pre-baseline testing, to reduce inter- and intra-individual variance due to subjects not fully understanding

the task demands (Goldberg et al., 2015); (ii) administration of alternative versions that are available for serial assessments (Benedict et al., 2012).

For the assessment of Cognitive-Motor Interference (CMI), patients were subjected to dual-task experiments for walking and balance. For gait assessment, patients performed the 2MWT in isolation without any interference (Gijbels et al., 2011). For balance, patients were asked to maintain their balance for 30 seconds as stable as possible on a force platform that recorded their postural sway (static posturography) while visually focusing on a point in front of them (single-task condition) (Cattaneo and Jonsdottir, 2009); and then repeated the posturographic assessment while performing the SCWT (Prosperini et al., 2016). In addition, patients underwent the TUG, for the assessment of dynamic balance.

MSIS-29 is a self-administered questionnaire that measures the physical (MSIS-29 PHY) and psychological impact (MSIS-29 COGN) of MS from the subject's perspective; it has been reported to be more sensitive than other quality-of-life scales in detecting rehabilitation-induced changes (Hobart et al., 2001). The MFIS-21 is a self-administered questionnaire based on items derived from interviews with individuals with MS about how fatigue impacts their lives; it includes three subscales: physical (MFIS-21 PHY), cognitive (MFIS-21 COGN) and psychosocial functioning (MFIS-21 PSY) (Téllez et al., 2005).

All eligible patients underwent an 8-week, five 30-minute sessions per week self-administered at-home training (total number of sessions: 40) and received a logbook to record daily training log (including time and type of game played) and training device (Nintendo ® Wii balance board, or tablet with COGNI-TRAcK).

All eligible patients were given a patient diary to record any AEs that occurred during the study and the occurrence of accidental falls, defined as unexpected contact of any part of the body with the ground that does not result from loss of consciousness. The occurrence and timing of adverse events (AEs), with a focus on accidental falls, provide data on the safety of home-based, minimally assisted interventions.

Interventions

Exergames represent a form of whole-body physical exercise performed through active video games. Playing exergames involves not only the hand-eye coordination, but also whole-body physical exertion, with the aim of improving fitness and promoting an active lifestyle (Read and Shortell, 2011b).

The training protocol was provided by the Nintendo ® Wii balance board and consisted of repetitions of several games selected from the "Wii Fit Plus" package (http:// www.wiifit.com/training/balance-games.html). Each game begins at basic level, and when a certain score is reached, patients is automatically moved to more advanced level. Patients were encouraged to play the next game if they have a level progress; otherwise, they are allotted 10 minutes for each game. During the first 4 weeks of training, patients were allowed to play only "Zazen" (sitting position), "Table Tilt" and "Ski Slalom"; later they added the remaining games "Penguin Slide", "Tightrope Walk", "Balance Bubble" and "Soccer Heading" (Prosperini et al., 2013).

COGNI-TRAcK is a low-cost, user-friendly application software (app) for portable devices (mobile phone and tablet) that delivers a self-administered, intensive, and monitored cognitive training based on working memory exercises. The main feature of COGNI-TRAcK is the implementation of automatic adaptive working load algorithms and procedures for intensiveness regulation. Moreover, it can be easily used at home enhancing the possibility to schedule an intensive training and ensuring adherence to treatment. Preliminary data showed that COGNI-TRAcK is highly usable, motivating, and well-accepted by patients with MS (Tacchino et al., 2015). Adaptive COGNI-TRAcK (i.e., automatic adjustment of tasks difficulty) has been found superior over sham COGNI-TRAcK (i.e., constant difficulty level) in verbal memory acquisition and delayed recall, verbal fluency, sustained attention, concentration, and information processing speed (Pedullà et al., 2016). Therefore, sham COGNI-TRAcK can be used as placebo-analogue arm to avoid ethical concerns and a possible unmotivating effect of wait-list group.

The Adaptive COGNI-TRAcK training protocol was provided by a dedicated app for mobile devices (cell phone or tablet). The app implements three different types of exercises (each performed for approximately 10 minutes per session),

consisting of a visuo-spatial working memory task, an N-back "operation" task, and an N-back "double" task. The adaptive training was structured such that the difficulty level of the exercises increased by one step each time the user performed a correct exercise. On the other hand, the difficulty level decreased by one step if the exercise was wrong three times in a row (Pedullà et al., 2016).

The Sham COGNI-TRAcK training protocol (placebo-analogue intervention) was provided by a dedicated app for mobile devices (mobile phone or tablet) as previously described for adaptive COGNI-TRAcK (Pedullà et al., 2016). However, the non-adaptive training consisted in an algorithm implementing two low difficulty levels alternating every day regardless of the user's performance.

Statistical Analysis

Overall, based on two previously published studies (de Giglio et al., 2015; Pedullà et al., 2016), the statistical plan was to randomize 126 patients (also considering a dropout rate of 20%). For the non-inferiority comparison, the null hypothesis is that the exergames intervention is inferior to the adaptive COGNI-TRAcK, while the alternative hypothesis is that the exergames intervention is not inferior to the adaptive COGNI-TRAcK by a predefined amount of SMDT score.

All analyses were based on the intention-to-treat principle, using the data set from the full analysis that included all randomized patients.

Efficacy data were analyzed by parametric and/or nonparametric repeated measures analysis of variance (RM-ANOVA). In each analysis, all measures or scores derived from the study assessments were considered as dependent variables; the three study visits (baseline, week 8, and week 16) as intra-subject factors; and the intervention arms (EXERGAMES, ADAPTIVE, and SHAM as inter-subject factors. Effect sizes were estimated as Cohen's F-squared, evaluated as small, medium, and large for values of 0.02, 0.15, and 0.35, respectively (Cohen, 1992).

EXERGAMES and ADAPTIVE were compared with SHAM as the placebo-analog arm. Therefore, all analyses were adjusted with Bonferroni's adjustment for multiple comparisons of 2-sided tests, yielding a significant 2-sided p-value of 0.025.

In this preliminary analysis, two different approach were followed.

As primary analysis, the changes from baseline of the SDMT over the treatment period (T1-T0) were compared in the 3 groups, using an analysis-of-variance models. The same analysis was performed for all the secondary outcome measures.

For the secondary analyses, 2-way mixed analysis of variance (ANOVA) tests, with group (3 levels) as between factor and time (3 levels: T0, T1, and T2) as within factor, were used. When the interaction factor timeXgroup was significant, the simple main effect of time was analyzed by means of three different repeated measure ANOVA tests, on the three groups separately. When the interaction factor was not significant, while the main effect of time was significant, pairwise comparisons with Bonferroni correction were tested.

P-values less than 0.05 in either direction were considered as significant. Analyses were carried out by using the Statistical Package for Social Sciences, version 25.0 (IBM SPSS, Chicago, Illinois).

Results

Start date for the study had been set for February 2019. However, due to the health situation given the SARS-COv-2 outbreak, the study start date was delayed until April 2020. A total of 69 patients were evaluated for eligibility in this pre-planned interim analysis; out of these, 47 (24 women, 23 men) with a mean age of 54.98 (18.35) years, mean MS duration of 15.4 (8.72) years, and median EDSS of 5 (2-6) were randomized to the three treatment groups. The three treatment groups were comparable in terms of baseline demographic and clinical characteristics (all p-values >0.2) (Table 8). Of the 22 patients who were not eligible for the study, 16 had an SDMT score > 38; 2 had a BDI-II score > 14; 3 were unable to maintain an upright position for more than 180 seconds; and 1 declined to participate in the study (Fig. 9).

Figure 10 shows the preliminary results on SDMT (primary endpoint) for the three treatment groups at baseline (T0) and after intervention periods (T1). Comparison of the changing from baseline at T1 in the SDMT showed statistically significant results between the SHAM group and the ADAPTIVE group (p=0.04). An improvement was observed between the EXERGAMES group and the SHAM group,

although not reaching statistical significance (p=0.06). Instead, comparison of the changing from baseline at T1 in TUG between the three groups showed a statistically significant improvement between the EXERGAMES group and the SHAM group (p=0.01) and the ADAPTIVE group (p<0.001) (Fig.11 and Table 9).

Regarding the assessment of fatigue, the comparison of the changing from baseline at T1 in the MIFS-21 showed statistically significant results between the SHAM group and the ADAPTIVE group (p=0.04), and between the ADAPTIVE group and the EXERGAMES group (p=0.01). Subscales of the MFIS-21 were also analyzed: the physical component (PHY MFIS-21), the cognitive component (COGN MFIS-21), and the psychosocial component (PSY MFIS-21). The comparison of change in PHY MFIS-21 between T0 and T1 showed statistically significant results between the SHAM group and the ADAPTIVE group (p=0.04); in COGN MFIS-21 statistically significant results emerged between the ADAPTIVE group and the EXERGAMES group (p=0.01). For the psychosocial component, however, no significant results emerged between T0 and T1 in the three groups (Table 9). In the EXERGAMES group, there was an improvement in balance measured by posturography between T0 and T1 in the ST and DT conditions (p= 0.01 and p=0.02), in contrast to the SHAM and ADAPTIVE groups.

To results of the secondary analysis can be seen in Table 10. For those measures in which the time*group interaction was statistically significant (SDMT, CVLT, BVMRT, TUG) the simple main effect of time was calculated for each group. Specifically, it was found that for the ADAPTIVE group, SDMT improved statistically significantly between T0 and T1 (p=0.04) whereas for the EXERGAMES group between T0 and T2 (p=0.035). Regarding BMVTR, in the ADAPTIVE group, statistically significant results were obtained between T0 and T1 (p=0.028), but not in the SHAM and EXERGAMES groups. With regard to TUG, however, only in the EXERGAMES group was there a statistically significant difference between T0 and T2 (p=0.010) and between T2 and T3 (p=0.001).

Considering the outcome with a not significant interaction factor, we found that the effect of time was significant in MSIS-29 TOT and MFIS-21 COGN. Post-hoc analysis showed that a statistically significant improvement was detected between T0

and T1 (p=0.019) and between T0 and T2 (0.04) for MSIS-29 TOT, and between T0 and T2 (p=0.012) and between T1 and T2 (p=0.007) in MFIS-21 COGN.

Finally, with respect to SCWT, 2MWT, MSIS-29 PHY, MSIS-29 COGN, MFIS-21 TOT, MFIS-21 PHY, MFIS-21 PSY and posturography in ST and DT, we did not find a statistically significant change over time.

Preliminary analysis of outcome predictors (CRIQ, HLAQ, and TCI) was not performed because of lack of data.

Table 8. Characteristics of Study Sample at baseline

		COGNI-TRAcK SHAM (n=15)	**COGNI-TRAcK ADAPTIVE (n=16)**	**EXERGAMES (n=16)**
Sex	W : M	8:7	9:7	7:9
Age	Years	55.84 (9.52)	47.54 (10.71)	51.87 (10.75)
BMI	kg	22.22 (6.63)	22.91 (2.79)	22.82 (2.88)
Formal education	Years	14.2 (3.6)	13.36 (2.5)	12.52 (3.8)
Disease Course	RR-MS	11	14	12
	SP-MS	3	2	4
	PP-MS	1	0	0
Disease duration	Years	15.56 (6.75)	16.77 (7.61)	13.56 (4.57)
EDSS score		5.5 [3.0-6.5]	4.5 [2.0-6.5]	4.0 [1.5-6.5]
DMT	None	4	1	0
	NTZ	4	6	4
	OCR	2	3	3
	FNG	1	1	0
	GLT	0	0	4
	TRF	3	1	3
	IFNB	0	3	0
	DMF	1	1	2
Symptomatic Therapy	Y:N	9:6	10:6	13:3
BDI-II		8.27 (8.69)	5.94 (6.79)	6.81 (8.94)
MMSE		28.87 (2.10)	27.81 (1.94)	27.94 (1.91)
SDMT		35.27 (3.36)	28.63 (8.09)	28.31 (9.14)

DMT Disease Modifying Therapy; NTZ Natalizumab; OCR Ocrelizumab; FNG Fingolimod; GLAT Glatiramer Acetate; TRF Teriflunomide; IFNB Interferon Beta; DMF Dimethyl Fumarate

Fig. 9. Flowchart

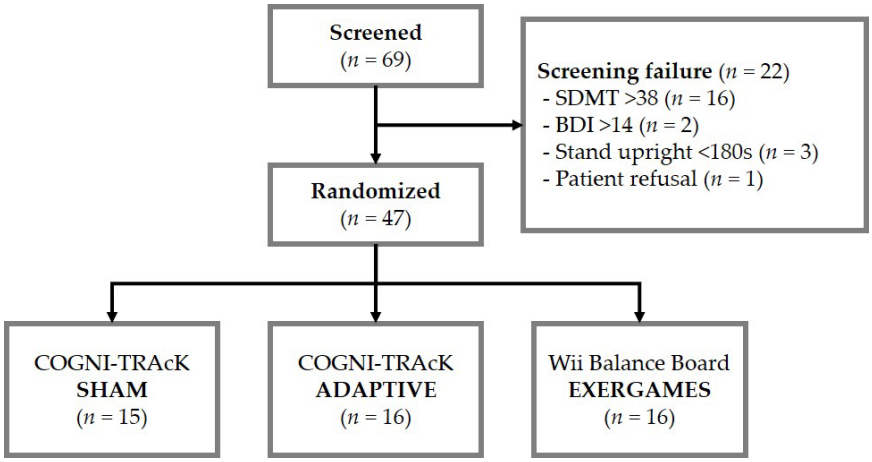
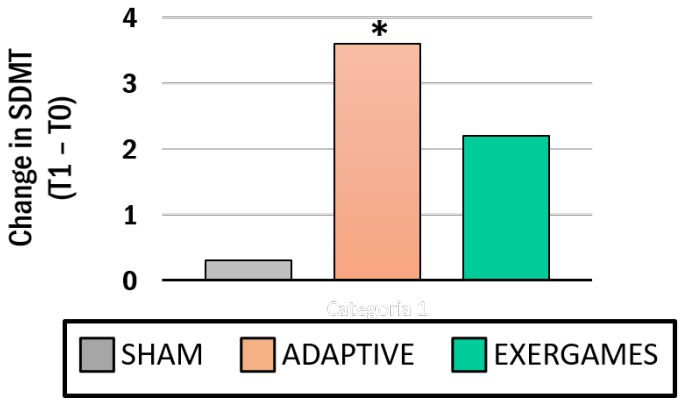
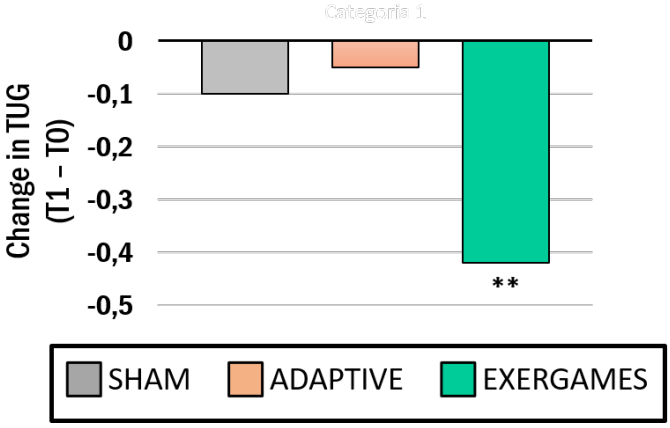


Fig. 10 Preliminary results between T0 and T1 of SDMT in three groups



* p <0.05 versus SHAM

Fig. 11 Preliminary results between T0 and T1 of TUG in three groups



** p <0.05 versus SHAM and ADAPTIVE

Table 9. Changing from baseline between T0 and T1 in assessment scale

	Group	Mean	SD	p	Post-hoc test		
					SHAM vs ADAPTIVE	SHAM vs EXERGAMES	ADAPTIVE vs EXERGAMES
Δ SDMT	**SHAM**	0.42	4.59	**0.05**	**0.04**	0.06	0.19
	ADAPTIVE	1.43	3.81				
	EXERGAMES	2.37	6.16				
Δ CVLT	**SHAM**	5.84	6.36	**0.01**	0.25	**0.003**	0.16
	ADAPTIVE	2.69	4.63				
	EXERGAMES	-0.80	4.69				
Δ BMVTR	**SHAM**	4.71	8.12	0.217	0.20	0.19	1.00
	ADAPTIVE	0.26	6.43				
	EXERGAMES	0.25	6.22				
Δ SCWT	**SHAM**	-0.50	4.45	**0.05**	0.71	**0.02**	0.15
	ADAPTIVE	1.06	3.33				
	EXERGAMES	4.75	7.33				
Δ 2MWT	**SHAM**	10.08	12.57	0.79	1.00	0.80	0.80
	ADAPTIVE	9.98	17.52				
	EXERGAMES	6.12	20.14				
Δ TUG	**SHAM**	-0.06	1.90	**0.05**	0.11	**0.01**	**<0.001**
	ADAPTIVE	-0.06	2.13				
	EXERGAMES	0.45	2.24				
Δ MSIS-29 TOT	**SHAM**	-5.04	18.79	0.99	1.00	0.99	0.99
	ADAPTIVE	-4.92	15.41				
	EXERGAMES	-5.34	9.71				
Δ MSIS-29 PHY	**SHAM**	-3.18	1374	0.61	0.59	0.99	0.56
	ADAPTIVE	2.37	21.02				
	EXERGAMES	-3.61	6.51				
Δ MSIS-29 COGN	**SHAM**	-2.07	9.57	0.80	0.91	0.92	0.73
	ADAPTIVE	-0.14	14.79				
	EXERGAMES	-3.90	14.01				
Δ MFIS-21 TOT	**SHAM**	-3.57	15.72	**0.008**	**0.04**	0.92	**0.02**
	ADAPTIVE	8.57	11.47				
	EXERGAMES	-5.46	10.40				
Δ MFIS-21 PHY	**SHAM**	-1.85	7.38	**0.04**	**0.04**	0.99	0.06
	ADAPTIVE	4.21	6.83				
	EXERGAMES	-1.53	4.61				
Δ MFIS-21 COGN	**SHAM**	-1.21	7.21	**0.007**	**0.05**	0.84	**0.01**
	ADAPTIVE	4.00	5.02				
	EXERGAMES	-2.46	4.82				
Δ MFIS-21 PSY	**SHAM**	-0.53	2.30	0.11	0.38	0.93	0.22
	ADAPTIVE	0.35	1.15				
	EXERGAMES	-0.76	1.59				

Table 10. Repeated measures ANOVA

	p (time)	p (time*group)	Post-hoc test T0 vs T1	Post-hoc test T0 vs T2	Post-hoc test T1 vs T2
SDMT	**<0.001**	**0.023**	0.31	**< 0.001**	**< 0.001**
CVLT	**0.02**	**0.007**	**0.049**	**0.032**	0.16
BMVTR	**< 0.001**	**0.001**	**< 0.001**	**< 0.001**	1.00
SCWT	0.16	0.19	0.15	0.85	0.37
2MWT	0.07	0.88	0.09	0.14	0.97
TUG	0.66	**0.01**	0.89	0.89	0.63
MSIS-29 TOT	**0.01**	0.15	**0.02**	**0.04**	0.94
MSIS-29 PHY	0.08	0.23	0.22	0.09	0.88
MSIS-29 COGN	0.08	0.28	0.08	0.84	0.25
MFIS-21 TOT	0.97	0.09	0.97	0.99	0.98
MFIS-21 PHY	0.82	0.08	0.80	0.94	0.94
MFIS-21 COGN	**0.004**	0.42	0.97	**0.01**	**0.007**
MFIS-21 PSY	0.04	0.07	0.83	0.71	0.38

Discussion

Despite the wide-ranging and demonstrated efficacy that disease-modifying therapies have in slowing MS progression, to date rehabilitation remains the only effective approach to reversing neurological disability and symptom exacerbation, managing deconditioning, and the resulting impairment of QoL in MS. With the introduction of International Classification of Functioning, Disability and Health (ICF) (WHO, 2001), the models of health and disability have been revolutionized towards a dynamic interaction between person and environment also in the pathological conditions, integrating health and non-health components, through a health and social multidimensional assessment of the person. Rehabilitation assumes a primary role in treating of diseases within ICF concepts, integrating clinical care and health-related QoL, in order to achieve the highest possible level of operation and participation in relation to the possibilities of the patient him/herself and him/her context.

Rehabilitation of people with MS is a multifactorial, active and dynamic assistance care, favoring the clinical stability, reducing disability and supporting the maintenance and recovery of a social active role. Physical exercise is the central component of the rehabilitation. The combination of its various use (type of exercise, frequency and time of the rehabilitation, intensity - FITT model) is the most comprehensive rehabilitation together with an adequate clinical and pharmacological monitoring and the structured educational and psycho-behavioral interventions (Cieza et al., 2004; Ward and Gutenbrunner, 2006). However, access to standard rehabilitation services can be difficult for patients (Chan, 2020). For this reason, rehabilitation providers are looking for "alternative strategies" that are as effective as standard rehabilitation, accessible to all, and inexpensive. Game-based rehabilitation meets all of these characteristics.

The use of technological rehabilitation devices for people with MS could overcome the barriers to accessing health care and provide specialized services to people with MS. It has been evident during this pandemic that we are experiencing. Rehabilitation is conventionally performed in an individualized setting during face-to-face meetings between the therapist and the patient as it is traditionally considered

a practical intervention. The possibility of using telemedicine services, even based on these devices, could provide services at home, in an attractive way.

The achieved results in this study and the development of the rehabilitation programs require scientific validation. The claimed benefits should be explored in longer follow-up assessments after the interventions. The confirmation of our preliminary data could suggest the use of exergames in improving cognitive strategies both: to access specialized services everywhere, and to provide rehabilitation opportunities for individuals with reduced mobility and transport limitations (Fjeldstad-Pardo et al., 2018).

Although this is only preliminary data, some interesting findings emerged from the study. First, it is worth noting that both patients treated with the COGNI-TRAcK and the Nintendo Wii had improvements at the SDMT compared to the SHAM group. While this was a previously known finding for the first type of intervention, with regard to exergames rehabilitation this is perhaps the first article to specifically address this. One possible explanation could stem from the fact that, through exergames it is also possible to improve a number of cognitive domains, such as planning, reasoning, and working memory, among others (Levin, 2011). Furthermore, the study found that patients who underwent home rehabilitation with the Nintendo Wii also achieved improvement in the motor domain. In fact, these patients improved in both static and dynamic balance. It would thus seem that rehabilitation training performed with exergames improves motor and cognitive domains, as described on the elderly population (Bavelier and Green, 2016; Bediou et al., 2018).

Second, it would appear that performing rehabilitation training with exergames may bring improvements in some specific domains of QoL and fatigue. The outcomes obtained for the fatigue in people with MS show that exergames are significantly effective in improving after intervention, compared to other groups. In the ADAPTIVE group, fatigue increased. Therefore, it is necessary to analyze the use of applications with increasingly complex cognitive exercises at the light of their possible impacts on the fatigue. The exergames present a positive impact on the

fatigue and on the cognitive function, as highlighted by the relationship with other assessment scales.

These findings have a several implications. The use of new, low-cost technologies has been developing more and more in recent years (Taylor and Griffin, 2015) to address the growing rehabilitation need of MS patients. Often rehabilitation programs focus almost exclusively on motor skills, leaving aside cognitive skills. The complexity of the MS means that patients present both cognitive and motor deficits, requiring an integrated rehabilitation approach. Rehabilitation with exergames requires simultaneous physical and cognitive effort from the patient, thus promoting not only the strengthening of motor functions, but also the efficiency of brain networks, especially those devoted to attention.

Through some intervention, exergaming incorporates most of the principles underlying experience-dependent neural plasticity (Kleim and Jones, 2008), such as high-intensity repetition of task-oriented exercises, incremental increases in task difficulty, real-time feedback, salience feedback, salience, motivation, and reward. In addition to the improvement in balance disturbances associated with functional and structural changes in cerebellar networks (Karim et al., 2012; Prosperini et al., 2014), it would thus appear that exergames also result in improvement in some cognitive functions.

As this is a preliminary analysis and still an ongoing study, the results obtained should certainly be taken with caution. In addition, the data analysis will need to be enriched by analysis of outcome predictors, and further analyses are needed to be performed to assess retention. Therefore, identifying new treatment strategies that are effective for both motor and cognitive improvement is relevant to counteracting the progression of disability and improving daily management.

In conclusion, preliminary analysis of the data collected thus far has yielded encouraging results. Indeed, approximately 37% of the estimated sample was enrolled. Our results suggest that only the exergaming group improved in both sustained attention and balance, supporting our a priori hypothesis suggesting the effectiveness of new technologies in the rehabilitation process for people with MS.

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