Physiotherapeutic methods for promoting neuroplasticity in patients with multiple sclerosis.

Avgerou M.D.[1], Evangelopoulou E.M.[2]
[1] *Postgraduate Training Program, 3rd Department of Orthopaedic Surgery, National and Kapodistrian University of Athens, KAT General Hospital of Athens, Greece.*
[2] *1st Department of Neurology, National and Kapodistrian University of Athens, Aeginition University Hospital, Athens, Greece.*

ABSTRACT

Multiple sclerosis (MS) is a disease of the central nervous system of autoimmune origin, characterized by inflammation, demyelination, gliosis (fibrous proliferation of the glial cells in the affected area) and finally, destruction of the neural cells (neural loss). Non pharmacological interventions for patients with MS focus primarily on physical and psychological rehabilitation.

Neuroplasticity can be defined as the ability of the brain to change, remodel and reorganize itself to obtain the ability to adapt to new situations. Although the concept of neuroplasticity is quite novel, it is one of the most important discoveries in neuroscience. The aim of the present scoping was to investigate and present the recent literature data regarding physiotherapeutic and other methods for promoting neuroplasticity in patients with multiple sclerosis.

In total, 102 relevant scientific papers (reviews, systematic reviews and original trials), published after 2010 were analyzed. The findings of the review are encouraging - a number of physiotherapeutic methods (such as therapeutic exercise or neurophysiological rehabilitation techniques, for example) appear to be effective in promoting neuroplasticity in patients with MS; on the other hand, the findings of newer and increasingly popular methods such as, for example, robotic – assisted rehabilitation are not clear.

However, as the relevant research is based on small and not always high quality clinical studies, it is clear that additional research is needed, with randomized controlled trials of sufficient statistical power in order to extract more solid scientific data.

Key – words: Multiple sclerosis, Neuroplasticity, Physiotherapy, Rehabilitation

Introduction

Multiple sclerosis (MS) is a disease of the central nervous system of autoimmune origin, characterized by inflammation, demyelination, gliosis (fibrous proliferation of the glial cells in the affected area) and finally, destruction of the neural cells (neural loss) [1]. Although, to date, the aetiology has not been clearly established, three main factors are thought to be involved in its pathophysiology: genetic factors, factors related to the environment and finally immune factors [2]. However, now the most likely etiology of the disease is considered a disimmunity mechanism caused by an autoimmune attack to the patient's central nervous system. A leading role in this process seems to be played by the CD4-positive (CD4+) lymphocytes; Th1 and Th17 effector cells are activated by an unknown antigenic trigger, causing the immune attack through cross-reactivity [3]. This is the "Outside-In" model, whereas, according to the "Inside-Out" model, an intrinsic abnormality of the central nervous system is the main factor triggering the inflammatory-mediated neural tissue damage [3].

It is estimated that more than 2.5 million patients worldwide currently suffer from the disease, with the vast majority of them being women (male to female ratio 3/1). The disease occurs for the first time primarily in the 20-40 age groups, although it can affect any age (typically, in 10% of cases it occurs early, before the age of 18) [4]. The three main features of MS are: (a) the formation of lesions in the central nervous system (also called plaques), (b) inflammation and (c) destruction of neurons' myelin sheath. These features interact in a complex way that is not yet fully understood, causing the breakdown of nerve tissue and this in turn causes the signs and symptoms of the disease [4].

Depending on the clinical course of the disease, MS is divided into seven main categories (groups) [5]: (a) relapsing – remitting (RR) group (70% - 80% of the patients), which is characterized by a relapsing course, (b) primary progressive (PP) group (15% - 20% of the patients), with a gradual and continuous deterioration of the clinical picture of the patient, but without the presence of corresponding relapses, (c) secondary progressive (SP) group, with slower and more gradual deterioration in comparison to the patients belonging to the primary progressive group, (d) progressive-relapsing (PR) group (5% of the patients), in whom there is a gradual worsening of the disease with intermittent periods of relapses, (e) clinical isolated syndrome (CIS), characterized by the occurrence of a single episode of central nervous system inflammation accompanied by demyelination, (f) fulminant disease, with severe symptomatology and rapid progression leading very quickly to a high degree of disability of the patient and finally and (g) benign disease, with mold symptomatology, rare relapses, causing mild disability to the patients.

As is evident from the above, the vast majority of MS patients belong to the relapsing-remitting category, in whom the relapses that occur gradually recover after weeks or even months, even without treatment; over time, however, the residual symptoms that remained after the relapses of the disease that did not fully subside accumulate, gradually increasing the patient's functional discomfort and disability [5]. The treatment of the disease and especially of the relapsing-remitting group is based on the administration of a number of drugs that have the potential to modify the course of the disease: these include, among others, glatiramer acetate, interferon-beta preparations, natalizumab, fingolimod, mitoxandrone and dimethyl fumarate.

Non-pharmacological interventions for MS focus primarily on physical and psychological rehabilitation. Non pharmacological-cognitive treatment involves aerobic training and exercise, interventions which aim to improve the quality of the patients' sleep, and neuropsychological rehabilitation, aiming aims both to improve cognitive disorders, and to increase patients' awareness of the deficits they have in performing activities of daily living [6]. Finally, among the innovative treatments applied in recent years are whole body cryostimulation [7], brain stimulation techniques such as the transcranial magnetic stimulation (TEMS) and the transcranial direct current stimulation (tDCS) [8] and even computer-based training programs [9]. The specific therapeutic methods aim, among other things, to improve the clinical picture of the patient through the stimulation of the plasticity of the central nervous system [6].

Neuroplasticity can be defined as the ability of the brain to change, remodel and reorganize itself in order to obtain the ability to adapt to new situations [10]. Although the concept of neuroplasticity is quite novel, it is one of the most important discoveries in neuroscience; the fact is that neural networks are not fixed, but their structure and function changes throughout the life at different levels such as: molecular structures, changes in gene structure, changes in gene expression and behavior depending on our experiences.

It was about 130 years ago when William James was

CORRESPONDING AUTHOR, GUARANTOR
Avgerou M.D., Postgraduate Training Program, 3rd Department of Orthopaedic Surgery, National and Kapodistrian University of Athens, KAT General Hospital of Athens, Greece. Phone number: +306974299784 Email: md.avgerou@gmail.com

the first scientist who introduced the theory of neuroplasticity in his "Principles of Psychology", were he proposed that the human brain is capable of continuous functional changes [11]. The term "neuroplasticity" was introduced for the first time in 1948, by Jerzy Konorski, a Polish neuroscientist; he proposed the theory that neurons that have been activated by a nearby active neural circuit change and integrate into that circuit [12]. Donald Hebb, a Canadian psychologist introduced "Hebb's rule", describing that any synchronized activity of two neurons can lead to the strengthening of their synaptic connections [13].

All these scientists had to fight against an academic society that did not accept the existence of neuroplasticity of the brain in adults, except in the developmental phase. Eric Kandel, who won the Nobel prize in Medicine in 2000 for his work on the neuroplasticity of the central nervous system stated that neuroplasticity has marked the last decade of the previous century (1990 – 2000), the "Decade of brain". His research in this area had begun as early as 1970, when he observed that in the simple brain of the marine snails, the chemical signals produced during the learning process resulted in definite changes of the structure of the neural synapses where these signals originated and terminated [14].

Two are the main types of neuroplasticity: (a) functional neuroplasticity, which is determined by the functions of memory and learning; it seems that during both of those functions of the human brain, permanent changes are established in the neuronal synapses, due to various intracellular biochemical processes [15] and (b) structural neuroplasticity, or synaptic plasticity, produced by complex changes in the intracellular synthesis of various proteins along with permanent changes in the number of the synaptic neurotransmitters [16].

The extensive and multilevel scientific research in the field of neuroplasticity that has been carried out over the past few decades has concluded that the human brain evolves and changes throughout an individual's lifetime; according to Demarin and Morovic (2014) [14], the great challenge for neuroscientists is to find and define the various neural pathways (both the major and the minor ones) who have the ability to support neuroplasticity of the compensatory circuits of the neural system. Although significantly damaged nerve cells do not have great regenerative capacity, there is now evidence that even after adulthood, neurons have the potential for varying degrees of circuit regeneration especially in those cases in which the significant barrier of the glial tissue can be narrowed, modified or even eliminated [17].

The aim of the present paper was to investigate and present the recent literature data regarding physiotherapeutic and other methods for promoting neuroplasticity in patients with multiple sclerosis. In order to achieve this objective, the tool of scoping literature review was chosen. Scoping review is a research method that follows a systematic way of approach, in order to capture, in the most possible comprehensive way, the scientific knowledge on a specific topic, identifying and recording the basic concepts, theories, sources of knowledge and, finally, the gaps that still exist [18]; it allows the researcher greater flexibility compared to systematic literature review and meta-analysis, as it is possible to present and interpret a wide range of published studies that address the research question, which have been conducted with different methods [19].

In order to carry out this literature review, a literature search was conducted in the following scientific databases: PubMed/NCBI, Cochrane Library of Systematic Reviews, Scopus, Nature and Science Direct. The key-words (mesh terms) used in the search engines of those databases were: *Mutliple sclerosis, MS, Neuroplasticity, Neuromodulation, Physiotherapy, Treatment methods,* in various combinations between them and with the use of the disjunctive terms AND and OR. The inclusion criteria for the published scientific papers were the following: (a) original clinical trials (randomized and non-randomized controlled studies and case series), narrative reviews as well as systematic reviews / meta-analyses of the literature, (b) publication date was later than 2010, (c) the language of publication is English and the full text of the article could be retrieved, (d) original trials, both clinical (in vivo) and experimental (in vivo), involving individuals of all ages and animals as well (in the experimental trials).

On the other hand, case reports and studies in which MS was not among the pathological conditions of the central nervous system studied were excluded.

Figure 1 presents the flow-chart of the scoping literature review, according to the principles of PRISMA [20]. In the following sections the findings of the literature review will be presented in detail.

Discussion

Initially, 1712 studies were identified after initial search on Pubmed internet database. After screening of titles and abstracts, (figure 1), 138 studies were included for final analysis in the present review.

The key factors that will determine the outcome of patients with MS are undoubtedly inflammatory demyelination along with axonal loss; the possibility of functional rehabilitation of these patients therefore depends primarily on the successful and at the same time sustainable repair of the damage that has already been caused, through the regression of inflammation, remyelination, and finally, the neuronal circuit functional reorganization [21,22]. According to Ksiazek-Winiarek et al., (2015) [2], the most likely molecular mechanisms that promote neuroplasticity in patients with MS are the following:

- *Brain derived neurotrophic factor (BDNF),* whose role is particularly important in the process of creating new and healthy nerve synapses,
- *Interleukine 1β,* whose role is important in the inflammatory processes of the CNS that develop in the context of MS,
- *Amyloid-*β_{1-42}, which also has a key role in the acute inflammatory process in the synaptic area,
- *Platelet-Derived Growth Factor (PDGF),* participating in the remission stages of the disease and finally,
- *Cannabidoid Type 1 Receptors (CB1Rs),* who are responsible for the reduction of the excessive glutamate-mediated excitation of the neuronal synapses [23].

In the following sections, the data of recently published original studies will be summarized in relation to specific physiotherapeutic methods that have the potential to promote neuroplasticity in patients with MS.

The role of exercise

Aerobic exercise seems to play an important role for the induction of neuroplasticity of the motor cortex. Garnier et al., (2017) [24], showed, in 12 healthy volunteers, that just submaximal (60% of the maximum heart rate) treadmill exercise increased the corticospinal excitability in just 30 minutes. Moti et al., (2017) [25], in a narrative literature review, showed that regular exercise may have positive effects in patients with MS in their balance, cognition, fatigue, depressive symptomatology, quality of life, quality of sleep, metabolic and cardiovascular co morbidities; moreover, the authors concluded that regular exercise might promote neuroplasticity on this particular group of patients. It seems that regular exercise and physical activity is essential in all patients with immune system diseases (including patients with MS) and treating physicians should recommend them daily regular exercise [26].

Feis et al., (2019) [27], in a randomized controlled study showed that just 12 weeks of regular exercise (three times per week) in terms of community-located jogging, improved, along with the aerobic capacity and the quality of life, the patients' visuospatial memory and pallidum volume. In another interesting prospective preliminary study the same year, on 12 patients with MS, Hoque et al., [28], showed that downslope walking, an eccentric exercise, promoted neuroplasticity (spinal excitability and walking function) of the patients. Stellmann et al., (2020) [29], in a randomized controlled study (57 patients with multiple MS) showed that just after three months of moderate-intensity exercise, there was an obvious increase of the functional connectivity of the brain hubs, which tried to compensate for the loss of the structural connectivity of the MS patients; this is therefore, according to the authors, a clear proof of the exercise-induced neuroplasticity in patients with MS, on the biological level. Furthermore, it appears that at a second stage, increased functional connectivity results in adaptive remyelination and oligodendrogenesis [30].

Chaves et al., (2020) [31], in a prospective pilot case series involving 10 patients with MS, who needed assistive ambulatory devices in order to carry out the activities of their daily living, showed that aerobic exercise (40 minutes walking using body weight, less than 10%, support), resulted in shorter length of the cortical silent period and increased motor evoked potential amplitudes. The main conclusion of the authors was that even in the group of MS patients who have a significant impairment of their mobility and

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functional capacity, the ability of neuroplasticity is preserved through systematic aerobic exercise; a further conclusion of the study was that patients' lower fitness levels and higher body fat levels were associated with limited exercise-induced enhancement of corticospinal excitability which is a specific biomarker of neuroplasticity [32]. Both the treating physicians and the patients' therapists should encourage systematic exercise and physical activity, through which not only the body, but also the CNS is trained [31].

In the same year, Devasahayam et al [33], in a prospective study including 10 patients with MS, showed that moderate to vigorous aerobic exercise (up to 65% of the maximum heart rate, 10 weeks for three sessions per week), in a room cooled to 16°C, improved fitness, walking speed and ability and quality of life; moreover, a statistical significant decrease in the value of serum IL-6 was noted, along with an increase in the value of brain-derived neurotrophic factor, which, as already reported, are important biomarkers indicative of the progression of neuroplasticity in MS patients [2].

Over the past few decades, Tai chi has gained increasing popularity as a therapeutic exercise method for treating a range of nervous system conditions including MS [34]. Liu et al., (2021) [35], in the context of a systematic review (24 in total, original papers) of the literature in relation to the effectiveness of this therapeutic method in the process of neuro-rehabilitation, concluded that (a) a number of proinflammatory biomarkers are reduced (IL-1,6,10,12, TNF, CRP), (b) a number of anti-inflammatory cytokines are increased (IL-10,13), (c) various oxidative factors are decreased (protein carbonylation, plasma 8-isoprostane and malondialdehyde) and (d) various neurotrophic factors are increased (BDNF, N-Acetylasperate). It is obvious that the Tai chi therapeutic method can offer multiple benefits in the process of neuro-rehabilitation, promoting neuroplasticity in patients with MS [35].

From all of the above mentioned, the significant effect of systemic physical activity and exercise on the promotion of neuroplasticity in patients with MS has been presented. These are findings which are broadly in line with the corresponding findings of the recently published systematic literature review by Sandroff et al., (2020) [36] regarding exercise training as a neuroplasticiy-inducing therapeutic method in patients with MS; the authors of the review stated that although this field of research is still in its infancy, with the few relevant studies involving only a small number of patients -only 10 original papers were included in the systematic literature review, most of them pilot studies, with a small number of participants -, the first, isolated results seem promising. It seems that there is indeed a tentative statement that exercise training has the potential to induce neuroplasticity in this particular group of patients [36] .

In another systematic literature review, Tavazzi et al., (2021) [37], investigated the efficacy of motor rehabilitation on the neuroplasticity, based on MRI markers of structural and in patients with MS; after analyzing 15 relevant original papers, they concluded that, although the small participants' numbers and the heterogeneity of the data, definite positive adaptive brain changes have been recorded, with are combined with a significant improvement in the clinical picture of patients. It is obvious that the MRI markers of functional and structural brain connectivity (such as the diffusion tensor imaging or the task-related and resting-state fMRI, should be introduced in daily clinical practice in order to accurately asset the neuroplasticity achieved in the context of motor training of MS patients and thereby to introduce or modify the rehabilitation protocols of the disease accordingly [37].

The role of robotic – assisted rehabilitation

One of the relatively most recent new therapeutic options in the arsenal of rehabilitation for a range of central nervous system injuries and pathologies, including MS, which began to be widely used in the 1990s is robotic – assisted physiotherapy. The use of specialized robotic devices enables the patient to achieve functional mobilization and ambulation, which is a very important element in all stages of rehabilitation [38]. The first published literature reviews did not clarify whether robotic – assisted gait training and body - weight supported treadmill training with the initially used rehabilitation robotic devices (especially the Lokomat device), were superior to the traditional physicotherapeutic approaches [39].

Straudi et al., (2017) [40], published the research protocol of a randomized controlled study involving 98 patients with progressive MS (the RAGTIME study), in order to compare the effectiveness of conventional physiotherapy versus robot – assisted gait training in this group of patients; among the outcome measures of the study were instrumental and circulating laboratory markers which were directly related to the promotion of neuroplasticity, such as the cortical activation, pro and anti-inflammatory cytokines and chemokines, coagulation, growth and neurotrophic factors. The results of the study published three years later [41], did not prove the superiority of robot-assisted gait training over the traditional intensive overground walking rehabilitation protocols in any of the study's outcome measures, including the neuroplasticity markers.

In one of the most recently published relevant papers, Adrowis et al., (2020) [42] conducted a pilot randomized controlled study, in 10 patients with MS in order to evaluate the effectiveness of the robotic exoskeleton REAER (Ekso-GT, Ekso Bionics, Inc) in the rehabilitation process of those patients; among to the outcome measures of the study was the brain connectivity (thalamocortical resting-state functional connectivity - RSFC), as it was measured by fMRI. The results of this small pilot study showed that there was a definite improvement of the thalamocortical RSFC, along with the patients' functional mobility, whereas no differences were found in relation to the patients' walking endurance. According to the authors, the improvements recorded on the MS patients' functional mobility were most probable due to integrative and adaptive central nervous system plasticity.

From all the above it is evident that scientific research in the field of robotic rehabilitation of MS patients, especially in the field of neuroplasticity, is still at a very early stage. The encouraging results of some pilot clinical studies [42], make it necessary to immediately design and conduct high quality randomized controlled studies with a large number of participants, in order to draw clearer conclusions.

The role of various other physiotherapeutic methods

Apart from rehabilitation programmes based on therapeutic exercise and robot-assisted rehabilitation, some studies have been published in recent years investigating the promotion of neuroplasticity after different types of physiotherapeutic interventions in patients with MS. In a narrative literature review, Flatchenecker (2015) [43], concluded that a number of physiotherapeutic interventions based on the neurophysiological principles (such as the proprioceptive neuromuscular stimulation, Vojta, Bobath, or even the newer constraint – induced movement therapy), have the ability to produce plastic changes to the MS patients' central nervous system, which over time are likely to have significant clinical benefits.

High – intensity rehabilitative task-oriented circuit training (TOCT) is one of those interventions, which aim to promote neuroplasticity through a number of exercises and tasks, which combine repetition, intensity and specificity. Straudi et al., (2014) [44], in one of the first relevant published randomized controlled trials, showed that after three months of a home-based TOCT exercise program the patients of the intervention group had a statistical significant improvement in their walking ability and their health – related quality of life.

Action observation training (AOT), is a relatively new physiotherapeutic intervention, whose use is aimed at improving the function of the upper limbs of patients with various neurological pathologic conditions, including MS [45]; Rocca et al., (2019) [46], in a preliminary randomized controlled study (41 patients suffering from MS and 46 healthy control participants), after a two week's AOT, found out with the use of functional MRI scans, definite effects in the frontal – temporal area of their brain, with no modifications of their white matter. At the same time, the clinical improvement recorded in the mobility of patients in the intervention group was directly correlated with the functional and volumetric MRI changes produced [46]. In the same year, Bonzano et al., [47], using an upper limb task – oriented motor training program in 30 patients with MS, showed that the patients in the intervention group had a more normal brain activation, with the activation clusters located mainly in the areas of the right cerebellum and the left hemisphere; those findings, based on functional MRI imaging, according to the authors show that this particular voluntary task – oriented exercises produces plastic changes to the MS patients' central nervous system towards a definitely more health pattern.

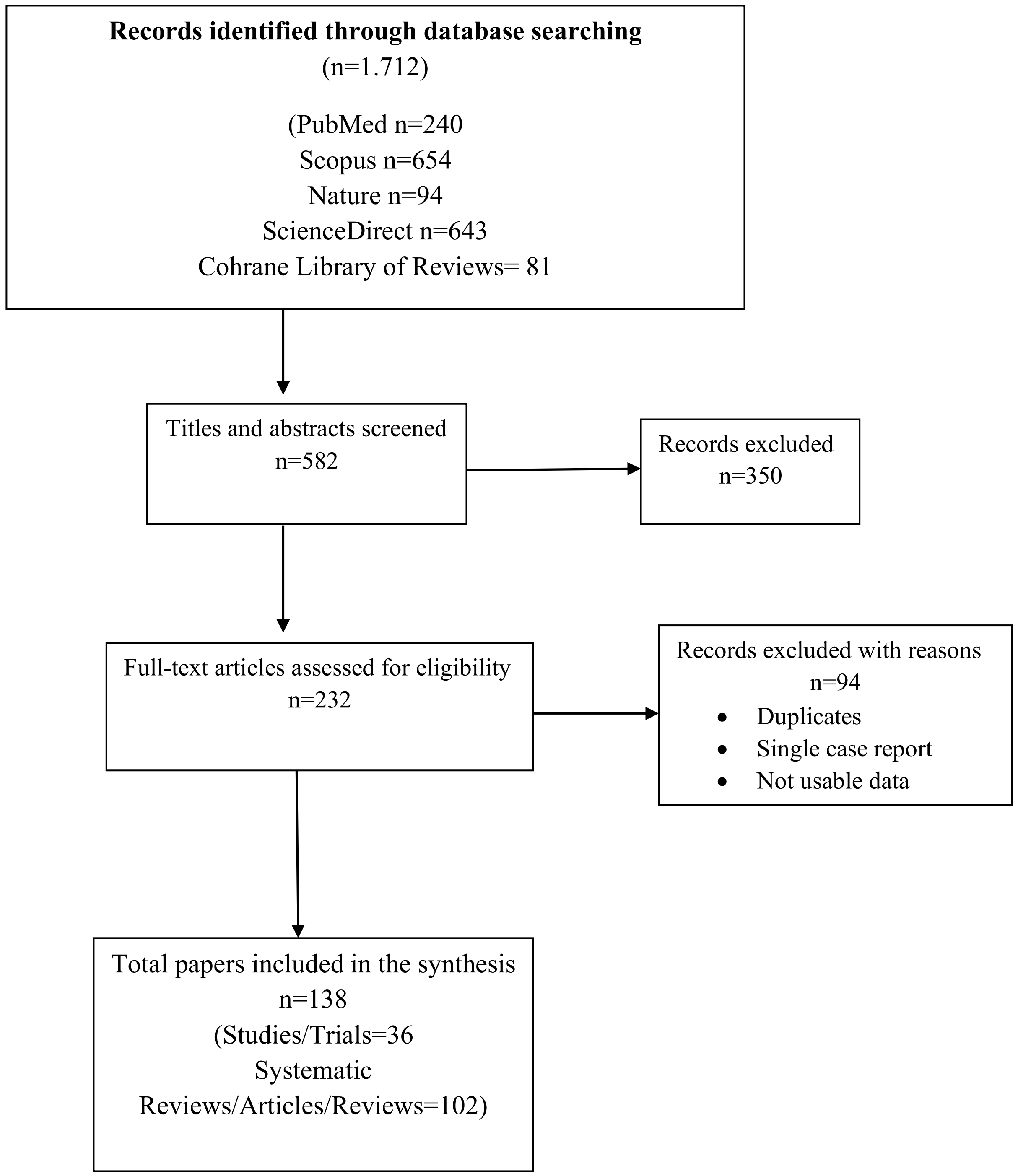

Figure 1: The PRISMA flowchart of the present scoping literature review

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One of the early symptoms of the disease, which significantly aggravates the clinical picture of the patients, is weakness of the respiratory muscles. Exercise has the ability to strengthen those specific muscle groups, improving the patients' respiratory function while at the same time promoting neuroplastic changes [48]. Huang et al, (2020) [49], showed that a 10 week's respiratory training using the Threshold Inspiratory Muscle Trainer method (IMT), produces statistical significant improvements in the inspiratory muscle strength in 36 non – ambulatory patients, being in advanced stages of MS; according to the authors, the specific overload principles of the method induce the neuroplasticity which in turn produces the favourable clinical outcomes.

The Assistive Device Selection, Training and Education Program (ADSTEP) is a multicomponent, progressive program of task – oriented walking aid selection [50]; Fling et al., (2019) [51], in a pilot study in 14 patients with MS who have already been using walking aids, showed, with the aid of functional MRI, that after just six weeks of ADSTEP, there was an increased functional connectivity between supplementary motor areas and both the putamen and the primary somatosensory cortices. These are, according to the authors, findings that clearly demonstrate that this specific way of rehabilitation and gait training of MS patients leads to specific modifications of central nervous system plasticity, with positive effects on the clinical progression of patients.

The Exergames therapeutic intervention (with the specific term coming from the combination of the words "exercise" and "games"), consists of exercising the whole body through the use of commercially available video games [52]. Prosperini et al., (2021) [53], published a systematic literature review and meta-analysis regarding the efficacy of the Exergames in balance dysfunction on patients suffering from various neurologic pathologies, including MS. The authors consider that among the mechanisms that explain the effectiveness of the method is the produced increasing efficiency of the attentional and executive brain networks, characteristic elements indicating plastic changes of the patients' central nervous system; furthermore, it was found that the effectiveness of the method depended mainly on the frequency of the Exergames exercise sessions and not so much on their duration or intensity.

Conclusion

Over the last two decades, the scientific community's knowledge on the plasticity of the central nervous system has increased significantly and continues to evolve to this day. It has become apparent that the long-held notion that the human brain is an organ which, after its initial rapid development, then gradually degenerates is not correct. On the contrary, in the healthy brain there are a number of complex mechanisms, collectively known as neuroplasticity, which attempt to resist the specific process of degeneration while at the same time adapting to the constantly changing conditions of the internal and external environment. Of course, this process is significantly altered, for the worse, in cases of severe acute and chronic diseases of the central nervous system, which significantly disturb all its physiological functions. Nevertheless, it seems that the function of neuroplasticity is maintained, in various degrees each time,trying to improve as much as possible the function of the brain.

This scoping literature review presented recent research data on the effectiveness of a range of physiotherapeutic methods in promoting neuroplasticity in patients with MS. The findings of the review are encouraging - a number of physiotherapeutic methods (such as therapeutic exercise or neurophysiological rehabilitation techniques, for example) appear to be effective in the associated field; on the other hand, the findings of newer and increasingly popular methods such as, for example, robotic – assisted rehabilitation are not clear. However, as the relevant research is based on small and not always high-quality clinical studies, it is clear that additional research is needed, with randomized controlled trials of sufficient statistical power in order to extract more solid scientific data.

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