**Neurological Diseases, Exercise and Balance**

**The Effect of Exercise Training on Gait, Balance, and Physical Fitness Asymmetries in Persons with Chronic Neurological Conditions: A Systematic Review of Randomized Controlled Trials**

**Background:** Persons with chronic neurological conditions (CNCs) often present with asymmetrical impairments, creating significant differences between contralateral limbs in body functions. These asymmetries have been associated with reduced mobility and balance, and are often targeted for reduction during rehabilitation. Exercise training has established benefits for persons with CNCs, and may have positive effects on asymmetry outcomes.

**Objectives:** The purpose of this review was to summarize the current evidence for the effects exercise training on gait, balance, and physical fitness asymmetry in randomized control trials (RCTs) of persons with CNCs.

**Results:** The search retrieved 3,493 articles, with 465 articles assessed for eligibly, and nine articles meeting the criteria for inclusion. Of the included articles, five incorporated resistance exercise, three incorporated aerobic exercise, and one incorporated combined exercise (i.e., resistance and aerobic exercise). Gait asymmetry improved significantly in four studies after resistance, aerobic, and combined exercise. Significant improvements in weight bearing asymmetry were reported in three studies after resistance exercise. One study reported significant improvements in both gait and balance asymmetry after resistance exercise.

**Conclusions:** Preliminary evidence suggests that exercise training, as a component of rehabilitation, may have positive effects on gait and balance asymmetry in persons with CNCs. Several limitations of the current literature were noted, including a limited number of studies, combination of exercise with other rehabilitation modalities, a lack of reporting on exercise prescriptions (e.g., number of repetitions, intensity), and variability in the calculation of asymmetry outcomes. These limitations prevent definitive conclusions on the effects of exercise training on asymmetry outcomes. Future trials are needed to determine the potential of exercise training for reducing asymmetry in persons with CNCs.

SOURCE: National Library of Medicine (National Institute of Health)

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7688661/>

**1. Introduction**

As reported by Hill and Polk [[9](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B9-genes-10-00720)], aerobic fitness (required for successful endurance activity), and aerobic capacity (measured as maximal oxygen consumption during exercise, VO2 max) correlate with brain size, both in humans and other animals

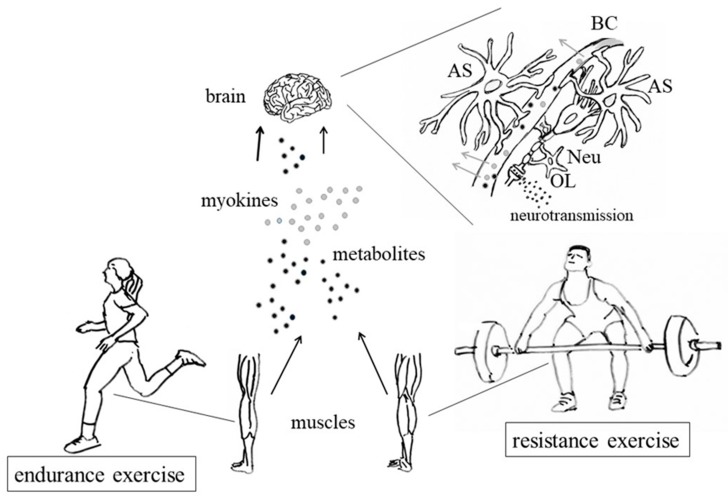
**2. Brain Plasticity, Adult Neurogenesis, and Physical Activity**

The brain capacity to adapt to ever-changing conditions, known as brain plasticity, depends on the ability of neurons to modify the strength and composition of their connections in response to both external and internal stimuli. The long-term potentiation (LTP) in synaptic efficacy constitutes the physiologic base for learning and memory. An important way for regulating neuronal function is the activity-dependent synapse-to-nucleus signalling, that can arise both in the post-synaptic and in the presynaptic element [[34](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B34-genes-10-00720),[35](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B35-genes-10-00720),[36](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B36-genes-10-00720),[37](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B37-genes-10-00720),[38](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B38-genes-10-00720)]. These signals are generated through different mechanisms, such as: (i) Calcium waves due to calcium-induced calcium release (CIRC) from the endoplasmic reticulum (ER) [[35](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B35-genes-10-00720),[39](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B39-genes-10-00720),[40](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B40-genes-10-00720)]; (ii) retrograde transport of proteins (e.g., **Jacob,** CREB Regulated Transcriptional Coactivator 1, **CRTC1**); Abelson-interacting protein 1, **Abi1**; the amyloid precursor protein intracellular domain associated-1 protein, **AIDA-1**; and the nuclear factor kappa-light-chain-enhancer of activated B cells, **NF-κB**); these proteins are post-translationally modified following synaptic activity, and transported to the nucleus, where they act on gene transcription, and thereafter on synaptic plasticity [[34](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B34-genes-10-00720),[35](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B35-genes-10-00720),[36](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B36-genes-10-00720),[37](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B37-genes-10-00720),[38](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B38-genes-10-00720),[41](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B41-genes-10-00720),[42](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B42-genes-10-00720)]; (iii) formation and microtubule-dependent trafficking of mRNA-protein complexes, that, after exiting the nucleus, move to neuronal periphery, where the mature transcripts localize in a repressed state, in response to local signalling, through activity-dependent activation of specific enzymes, the regulatory proteins can be then modified, for example, by phosphorylation, and the mRNAs can be translated; some of the newly synthesized proteins can accumulate at the synapse, while others can shuttle back to the nucleus to modify chromatin structure and expression [[43](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B43-genes-10-00720)].

By regulating synapse-to-nucleus signalling, all these events are crucial for allowing synapse activity to result in the specific gene expression programs necessary for learning and memory. In agreement with this idea, the impaired function of these signalling proteins brings about intellectual disability, psychiatric disorders, or neurodegeneration [[37](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B37-genes-10-00720),[38](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B38-genes-10-00720),[42](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B42-genes-10-00720)]. On the other hand, we can hypothesize that an increase of their function, for example as a response to PA, could also enhance brain functions and plasticity.

In the past, it was generally accepted that new neurons could not be generated in the adult to replace dying cells, and this limitation was also considered to be the main cause of neurodegeneration as well as of cognitive decline in the elderly population. However, since the 1960s, many researchers presented data suggesting that, in all the mammals analysed, new neurons could be generated in the sub-granular zone (SGZ) of the dentate gyrus of the hippocampus, and in the sub-ventricular zone (SVZ) of the lateral ventricles, in the postnatal and adult life [[44](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B44-genes-10-00720),[45](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B45-genes-10-00720),[46](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B46-genes-10-00720),[47](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B47-genes-10-00720),[48](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B48-genes-10-00720),[49](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B49-genes-10-00720),[50](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B50-genes-10-00720)]. In particular, neurons born in the SGZ were shown to differentiate and integrate into the local neural network of the hippocampus. These findings are extremely important since the hippocampus is fundamental for the formation of certain types of memory, such as episodic memory and spatial memory [[51](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B51-genes-10-00720),[52](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B52-genes-10-00720),[53](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B53-genes-10-00720),[54](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B54-genes-10-00720)]. In addition, hippocampus-dependent learning is one of the major regulators of hippocampal neurogenesis [[55](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B55-genes-10-00720)]: living in environments which stimulate learning enhances, in rats, the survival of neurons, born in the adult from neural stem cells (NSCs) [[52](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B52-genes-10-00720)].

Now, increasing evidence suggests that PA, largely due to factors released by contracting muscles ([Section 3](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#sec3-genes-10-00720); [Figure 1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/figure/genes-10-00720-f001/)), can improve brain functions, such as memory and attention, in both children and adults [[56](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B56-genes-10-00720),[57](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B57-genes-10-00720),[58](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B58-genes-10-00720),[59](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B59-genes-10-00720),[60](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B60-genes-10-00720),[61](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B61-genes-10-00720),[62](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B62-genes-10-00720),[63](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B63-genes-10-00720),[64](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B64-genes-10-00720)]. A few examples of single studies (first three rows) and reviews/meta-analyses (second three rows), aimed at ascertaining any relationship between PA and learning/memory, are given in [Table 1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/table/genes-10-00720-t001/).

[[](https://www.ncbi.nlm.nih.gov/core/lw/2.0/html/tileshop_pmc/tileshop_pmc_inline.html?title=Click%20on%20image%20to%20zoom&p=PMC3&id=6770965_genes-10-00720-g001.jpg)](https://www.ncbi.nlm.nih.gov/core/lw/2.0/html/tileshop_pmc/tileshop_pmc_inline.html?title=Click%20on%20image%20to%20zoom&p=PMC3&id=6770965_genes-10-00720-g001.jpg" \t "tileshopwindow)

[Figure 1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/figure/genes-10-00720-f001/)

Hypothetical pathway for the exercise-mediated effects on brain functions: both endurance and resistance exercise, even if with different kinetics and properties, allow muscle synthesis, and release myokines (e.g., brain-derived neurotrophic factor, BDNF), as well as of metabolites (such as lactate) into the circulation; these molecules can cross the blood­­­­–brain barrier (BBB) at the level of the brain capillaries (grey arrows) and affect the functions of both neurons and glial cells, thus modifying neurotransmission in different regions of the brain. As explained in the text, neurotransmission can then activate pathways leading to modifications of gene expression. AS: astrocytes; BC: brain capillaries; Neu: neurons; OL: oligodendrocytes.

Table 1

Effects of physical activity (PA) on learning and memory in children and adolescents. In the first three rows single studies are reported, while the second three rows refer to reviews/meta-analyses. In the “Conclusions” column, the main results of the analyses, as well as a few comments on them, are given.

| **Protocol/Aims [Ref]** | **Subjects/Studies Included** | **Methods of Analysis** | **Conclusions** |
| --- | --- | --- | --- |
| Analysis based on a randomized controlled trial (Ballabeina Study: [[65](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B65-genes-10-00720)]) aimed at evidencing any relationship between aerobic fitness/motor skills and working memory and attention in pre-school children [[59](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B59-genes-10-00720)] | 245 ethnically diverse pre-school children (49% girl, mean age 5.2 years) were analysed at the beginning of the activity and 9 months later. | Physical tests: 1. Aerobic fitness, assessed according to the 20 m shuttle run [[66](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B66-genes-10-00720)], 2. Agility, assessed by an obstacle course, 3. Dynamic balance on a beam. In order to evaluate spatial memory and attention, each child was tested individually by focused tests. | **Higher baseline aerobic fitness and motor skills were related to higher levels of working memory and attention.** A further improvement of these latter abilities was noticed in the following 9 months. |
| The aim of the study was to ascertain whether very low-intensity exercise (i.e., walking), practiced during foreign-language (Polish) vocabulary encoding, improves subsequent recall, in comparison with encoding during physical rest [[62](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B62-genes-10-00720)] | 49 right-handed, monolingual, Germans, healthy subjects (aged 18–30 years). Criteria of exclusion: a history of psychiatric or neurological disorders, smoking, obesity, and any knowledge of Polish or other Slavic languages. | In the first session, participants learned 40 Polish words while walking on the motor-driven treadmill, at their previously determined preferred rate. In the second session, the participants learned a further group of 40 words, while sitting in a chair. Each session lasted 30 min. The order of sessions was different for different subjects, in a balanced way, and the experiments were repeated twice. | In both experiments, participants’ **performance was better when they exercised during learning** compared to learning when sedentary. Serum BDNF levels and salivary cortisol concentration were also measured: serum BDNF was unrelated to memory performance; on the other hand, a positive correlation between the salivary cortisol and the number of correctly recalled words was found. |
| The aim of the study was to clarify whether mnemonic discrimination is improved by an acute bout of moderate-intensity aerobic exercise [[63](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B63-genes-10-00720)] | 21 healthy young adults (mean age 20.5 ± 1.4 years, 10 females), without histories of neurological or psychiatric disorders. All participants had normal or corrected-to-normal vision, and normal colour vision. | In this study moderate intensity is defined as 40–59% of V̇O2 peak, as established by the American College of Sports Medicine (ACSM) [[67](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B67-genes-10-00720)]. The activity was performed by a recumbent ergometer. Mnemonic task: the participants were first shown 196 pictures of everyday objects and asked, for each of them, whether it was an indoor or an outdoor item. Then they were asked to identify by pressing a button, in the second group of 256 items, which were ‘previously seen’, ‘similar but not identical’ or ‘not previously seen’. | **The lure discrimination index (LDI) for high-similarity items was higher after 10 min of moderate aerobic exercise** than in resting controls, thus suggesting that a bout of acute aerobic exercise could improve pattern separation, that seems to rely on the dentate gyrus (DG) in humans. |
| The aim of the analysis was to search the literature, looking for evidence of chronic PA effects on mental health in children and adolescents [[58](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B58-genes-10-00720)]. | Review articles reporting chronic physical activity and at least one mental health outcome (i.e., depression, anxiety/stress, self-esteem and cognitive functioning) in children/adolescents. Reviews chosen: 4 papers on the evidence concerning PA and depression; 4 for anxiety; 3 for self-esteem; 7 for cognitive functions. | Analysis based on data collected from PubMed, SPORTDiscus, PsychINFO, Web of Science, Medline, Cochrane Library, and ISI Science Citation Index, by using search terms related to the variables of interest (e.g., sport, exercise, physical activity) and mental health outcome variables (e.g., depression, anxiety, self-esteem, cognitive functioning). | **Associations between PA and mental health in young people (Tables 1–4 in Ref. [**[**58**](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B58-genes-10-00720)**]) is evident, but the effects are small-to-moderate, probably because of weakness of the research designs.** Small but consistent association between sedentary time and poorer mental health is also evident. |
| The aim of this systematic review was to find out studies elucidating the relationship between aerobic PA and children’s cognition, academic achievement, and psychosocial function [[60](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B60-genes-10-00720)] | Studies analysed concerned interventions of aerobic PA in children younger than 19 years. Only randomized control trials that measured psychological, behavioural, cognitive, or academic outcomes were included. | The review was performed using MEDLINE, Cochrane, PsycINFO, SPORTDiscus, and EMBASE. Additional studies were identified through back-searching bibliographies. | **Aerobic PA is positively associated with cognition, academic achievement, behaviour, and psychosocial functioning outcomes.** **More rigorous trials, however, required for deducing detailed relationships.** |
| Systematic review and meta-analysis of studies concerning associations between PA/sedentary lifestyle and mental health. Meta-analyses were performed in randomized controlled trials (RCTs) and non-RCTs (i.e., quasi-experimental studies) [[64](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B64-genes-10-00720)] | Studies published from January 2013 to April 2018. Studies were included if they comprehended PA or sedentary behaviour data and at least one psychological ill-being (i.e., depression, anxiety, stress, etc.) or psychological well-being (i.e., self-esteem, optimism, happiness, etc.) outcome in pre-schoolers (2–5 years of age), children (6–11 years of age) or adolescents (12–18 years of age). | Analysis based on data collected through a systematic search of the PubMed and Web of Science databases by two independent researchers. A narrative synthesis of observational studies was conducted. | **PA improves adolescents’ mental health, but additional studies are needed to confirm the effects of PA on children.** Findings from observational studies, however, suggest that promoting PA and decreasing sedentary behaviour might have a protecting effect on mental health in both children and adolescents. |

[Open in a separate window](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/table/genes-10-00720-t001/?report=objectonly)

The data reported in [Table 1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/table/genes-10-00720-t001/) clearly indicate that PA has a positive effect on mental health and abilities, especially in adolescents; however, as reported in the “Conclusions” column (sentences in bold letters), most authors agree on the fact that the previous studies do not yet give uniform indications on the relationships between the type/intensity/frequency of exercise and the brain health outcomes; these limitations derive, on one hand, from the wide range of conditions set in the exercise programs, and on the other hand, the differences from study to study also depend on the variability of the parameters chosen to evaluate mental health. We also have to add to these considerations the poor knowledge we still have of ‘mind’ and of ‘mental health’. Thus, many laboratories are now focusing on exercise-dependent cellular and molecular modifications of brain cells activity, in the attempt to uncover the mechanisms underlying PA–mental health biochemical relationships.

At the cellular level, it was found that treadmill exercise can increase hippocampal neurogenesis in aged mice [[68](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B68-genes-10-00720)]. Interestingly, exercise can also affect the proliferation [[69](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B69-genes-10-00720),[70](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B70-genes-10-00720)], as well as size and function, of astrocytes [[71](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B71-genes-10-00720)]. These latter events regulate, in turn, the number and localization of neuronal synapses, and might influence LTP and episodic memory formation [[72](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B72-genes-10-00720)].

Many researchers suggested that all these effects are also regulated by the brain capillaries (BC, [Figure 1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/figure/genes-10-00720-f001/)) that reach the neurogenic niche, supplying angiogenetic growth factors, such as the growth and differentiation factor 11 (**GDF11**), the vascular endothelial growth factor (**VEGF**) [[59](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/#B59-genes-10-00720)], and **BDNF**, that activates a cellular survival pathway

SOURCE: National Library of Medicine (National Institute of Health)

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770965/>