

Advancement In Neuroplasticity Trainings in Multiple Fields Since 2018

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Abstract. Neuroplasticity training is a rapidly growing practice that has great potential in the treatment of neurological diseases and disorders. This review aims to discuss the advancements in neuroplastic training in the form of motor, auditory, and other training methods. Neuroplastic training has seen promising results in patients encompassing a wide range of ages and conditions. Improvements in parameters such as executive function, gray & white matter, neuronal connectivity, neuron excitation, mini mental state examination (MMSE) score, activities of daily living (ADL) score, and others were observed. The training methods and results are summarized and organized into a table in the review.

Keywords: Neuroplasticity, Training, Motor, Auditory

1. Evolution of Neuroplasticity in Science

Neuroplasticity is the brain's ability to modify and reform itself over the course of time. The field began as a study to challenge the old dogma of neuroscience research, with the earliest studies showing the core principle that the amount of neurons in the brain is not a set amount, and can change over time. In a more general sense, neuroplasticity refers to "the ability to make adaptive changes related to the structure and function of the nervous system" [1]. As a result, neuroplasticity is not limited to just morphological changes such as changes in connections between neurons and the growth of new neurons. Neuroplasticity can also refer to chemical changes in the brain's ecosystem. Historically, studies on neuroplasticity were largely focused on how the brain changes as a result of stimuli and growth [2]. This could include injuries, but also positive stimuli. However, neuroscience as a whole was not as attractive in the past. Research faltered for a number of reasons. It was difficult to acquire subjects and cases to study the brain, and it was difficult to measure things empirically, with studies often relying on neurological tests and scoring systems as opposed to measuring certain chemical compounds or other more reliable parameters.

Nowadays, with the advent of MRI and more sophisticated technology, neuroscience has observed great improvements in understanding and applications. One of the most important applications of neuroscience is understanding neurological disease, as well as how to combat it. Many studies have approached the problem of neurological disease through a pharmaceutical approach. However, there are many issues. The main issue is the blood brain barrier, which heavily limits the amount of ways in which a drug may be administered. There is also the issue of the brain's secluded nature, which is far different from the circulatory and excretory systems that most drugs are designed with in mind. It is also difficult for drugs to reach their target once inside of the brain fluid, amongst many other difficulties with the pharmaceutical approach [3]. As a result, neuroplasticity represents a promising new avenue in the battle against neurological disease.

Neuroplasticity offers a different approach to understanding diseases in the brain. Rather than drugs or other invasive therapies, it could be possible to induce the brain to repair itself. Many diseases are caused as a result of morphological difficulties, such as loss of neuron connections [4]. Naturally, neuroplasticity could solve this problem. Of course, many diseases also have a biochemical element, such as amyloid plaques in Alzheimer's, [5] but neuroplasticity represents a promising addition to treatment options. This is especially important due to the difficulties of a pharmacological approach. It is extremely difficult to design a drug that does not affect the brain's ecosystem, as it is necessary for the chemical component of interest to not get swept out of the brain by its cleaning

mechanism in order for the drug to function. As a result, lingering molecules build up over time, representing dangerous side effects [6]. On the other hand, using less invasive drugs leads to higher dosages and prolonged treatment periods due to low efficacy. For these reasons, neuroplasticity training could be the missing piece that fills in the gaps of main line drugs. Recent studies on neuroplasticity training have shown just that. Clinical trials on children and adults of a large age range have shown improved gray and white matter masses, as well as improved scores in a multitude of neurological tests [7-9]. Such trials have been performed in hospitals, institutions, and from the participant's own homes. The therapies of interest are generally very low-risk and non-invasive. They have also been compared with conventional western medicines for neurological disorders, such as donepezil [10].

Motor training in neuroplasticity is by far the most popular and potentially beneficial form of training. Many neurological disorders result in failures in motor control in multiple areas, including the limbs, torso, waist, spine, and other areas of the body. For this reason, a one-size-fits-all approach utilizing motor training could be a breakthrough in multiple fronts at a relatively low cost. Many recent studies have utilized unique training techniques, including virtual reality simulations, computer games, and robotic exoskeletons to help patients improve cognitive ability [7,11,12]. These studies aim to target the coordination of the brain with motor neurons and improve neurological connectivity. Surprisingly, they produced similar results to more conventional studies that focused on exercise in different formats [13,14].

Other forms of training like auditory training and memory training are also tested in research and therapies regarding neuroplasticity. For example, auditory training has been used to target linguistic disorders and memory loss [15]. One of the greater difficulties we face is the lack of effective treatment options for linguistic disorders. Issues affecting the language centers in the brain heavily impair an individual for life. While many cases are a result of physical damage, failure to learn language at a young age can occur [16]. Auditory training can greatly improve the related linguistic areas in the brain in terms of brain matter and neuron connectivity [15].

In this review, I summarized recent studies on training related to neuroplasticity in motor, auditory, and memory ability. The purpose of this review is to serve as a guide for future studies and research on neuroplasticity and the related fields by providing examples and procedures, as well as the results and effectiveness of the training methods.

Table 1. Summary of trainings in different fields of research in neuroplasticity

Fields of Study	Subjects	Methods	Results	Citations
Motor	Chronic Stroke Patients	Transcranial direct current stimulation	Improved corticospinal excitability	[17]
Motor	Children (Diplegic Cerebral Palsy)	Gross Motor Intervention Program	Primary Gross Motor Skill Measure Score increase	[7]
Motor	Chronic Stroke Patients	VR Motor Control Training, Serum Biomarkers	AROM-Elbow Extension, Serum Time Effects, AROM Forearm Pronation, Misc Clinical Assessments	[8]
Motor	Healthy Older Adults	Aerobic Exercise (walking & dance)	Positive white matter changes	[9]
Motor	Stroke Patients	Physical therapy,	Fugl Meyer upper extremity	[18]

		Rejoyce gaming system	(FMUE), Brunnstrom stages of stroke recovery (BSSR), Stroke specific quality of life scale (SSQOL) improvement. BSSR of the hand only improved in the gaming group.	
Motor	Stroke Patients	Wrist-Joint robotic exoskeleton, conventional upper-limb rehabilitation	Improved motor outcomes and cortical-excitability, slightly better results from robotic exoskeleton group	[12]
Motor	Preschool children with cerebral palsy	Hand-arm bimanual intensive therapy including lower extremities, normal motor activity	Protocol Only	[19]
Motor	Parkinson's Patients with Freezing Gait	Resistance training group, traditional motor rehabilitation group	Only adaptive resistance training improved all outcomes (freezing of gait ratio, motor signs, quality of life, and more), seems more effective than traditional motor rehabilitation	[13]
Motor	Adults with risk of Alzheimer's or other dementias	Ballroom dancing group, Treadmill walking group	Composite executive function score from digit-symbol substitution, flanker interference, and walking-while-talking tasks, and functional neuroplasticity during fMRI-adapted versions of the previous outcomes	[20]
Motor	Stroke patients	Standard physical therapy, high-frequency repetitive transcranial magnetic stimulation, low frequency rTMS	Motor improvement far larger in rTMS groups than control, HF-rTMS showed far higher cortical-excitability and motor-evoked fMRI activation,	[14]
Auditory	Stroke Patients	Vocal Music & Instrumental Music Intervention	Improvement in functional connectivity in left inferior parietal areas. Improved verbal memory in vocal music group	[15]
Auditory	Retired elderly	Piano instruction, musical listening awareness	Protocol Only	[21]
Auditory	Stroke patients	Listening of	Vocal music enhanced	[22]

		instrumental music, vocal music, and audio books	language recovery and verbal memory recovery the most, increased gray matter volume in left temporal areas	
Auditory	Traumatic brain injury patients	Neurological music therapy intervention	Gray matter volume in right inferior frontal gyrus increase significantly, executive function improvement	[23]
Other	COVID-19 Patients	Hyperbaric oxygen therapy	Improved global cognitive function, attention, executive function, energy, psychiatric symptoms, and pain interference	[24]
Other	mTBI & Cognitive Impairment	Computerized cognitive training program, computer games as control	Cognitive function improvement vs control	[11]
Other	Stroke patients	Conventional physiotherapy, Neurorestoration protocol	Improvement in all factors using Berg Balance Scale, Barthel Index, Balance and functional performance improvement is statistically significant in neurorestoration group	[25]
Other	Depressed Outpatients	Aerobic Exercise, adjunct exercise treatment	Protocol Only	[26]

2. Motor Training

Motor training largely focused on stimulating related neurons. Many motor impairments could greatly benefit from functional neuroplastic changes that result from special training methods. However, the mechanisms of neuroplastic motor training are poorly understood. Current research aims to completely understand how different training methods can target different regions of the brain, as well as how neuroplasticity can be harnessed on a case-by-case level of specificity.

2.1. Neuroplasticity in Diplegic Cerebral Palsy

Diplegic Cerebral Palsy (DCP) is characterized by atypical sensorimotor connectivity and function. The symptoms of DCP include development and movement impairments, most commonly manifesting in a difficulty to walk. The causes of DCP, the alterations in the brain, can be extremely diverse. Bilateral lower limb corticospinal tract projection from the primary motor cortex (M1) is highly involved. Generally, CST connectivity goes across the body from the M1 in one hemisphere to the other side of the body. However, in DCP, lower limb projections can result from either M1. M1 activation in both hemispheres has been observed in unilateral lower limb movement as well [27]. Currently, much of neuroplasticity research in cerebral palsy has been focused on the upper extremity, or upper limbs of the body. M1 activity is determined by a laterality index, which uses the ratio of activity between the contralateral and ipsilateral M1s [28]. An increased ratio of contralateral M1

activity is associated with improved outcomes of the affected limbs for children with unilateral cerebral palsy [29]. Studies within the past decade have laid the groundwork for evidence-based upper limb therapies, which are flexible training options depending on the patient's specific condition [29,30,31]. Non-invasive methods have also been considered. The same trend is not observed in lower limb research, but recent studies have begun to shed light on non-invasive options for lower limb therapy.

Lower extremity strength training interventions are observed to improve lower limb M1 function. Such interventions include movement skills such as running, jumping, and kicking. Hilderley et al. produced fMRI data that greatly supported the idea that lower limb M1 activity improved. Motor skills assessment in the study included running in bursts and stopping accurately, foot-to-foot dribbling a soccer ball down a track, and moving between pylons while walking or running. Goals were assessed using the Canadian Occupational Performance Measure (COPM) and a 1-10 rating scale. The study saw a significant increase in contralateral activity following intervention for the ankle on the dominant leg [7].

In one other study, hand-arm bimanual intensive therapy including lower extremities (HABIT-ILE) was proposed to combine both upper and lower extremity training. The effects of HABIT-ILE, especially on cerebral palsy in young children, are not well understood in terms of functional, biochemical, and neurological changes. Currently, the study is discussed as a randomized controlled trial, and only exists as a protocol. The researchers expect that HABIT-ILE will produce positive functional, biochemical, and neurological outcomes, and impact the overall development curve of the children [19].

2.2. Neuroplasticity in Alzheimer's & Related Dementias

Alzheimer's and related dementias (ADRD) are one of the most common neurological diseases. Common symptoms include memory loss, poor judgment, confusion, difficulty speaking and writing, and other cognitive deficits. Modern understanding of these diseases is mainly molecular, with a pharmacological approach attracting many researchers in the hopes of combating mechanisms of disease development. These include things like oxidative stress in the brain and toxic oligomers [5]. With the development of neuroscience and the introduction of neuroplasticity, neuroplastic training is now being considered as a side-by-side treatment.

Multiple studies have found positive results from aerobic exercise interventions in the context of Alzheimer's and related dementias. Activities such as walking and assisted arm movements have been found to improve executive functions and mini-mental state examination (MMSE) scores [13]. New studies and protocols aim to expand on these positive effects and induce greater neuroplastic reformation. In one pilot clinical trial protocol, social dancing is proposed to be more effective in improving executive function than aerobic exercise without a social/cognitive element, such as simple arm/wrist movement therapies [20]. Executive functions (EF) include those that coordinate complex behaviors, such as planning, reasoning, attention allocation, and selection/inhibition of actions. These are generally negatively affected by the aging process, cognitive impairment, and Alzheimer's and related dementias. Blumen et al. aimed to improve executive function via aerobic exercise interventions. It was hypothesized that neuroplastic restructuring of the hippocampal and prefrontal cortex regions would improve executive function. Training interventions included social dancing (intervention) and walking (control) to determine whether exercising with social interactions would improve neuroplasticity. EF score was determined using the DSST, flanker interference, and WWT tasks. Neuroplasticity was assessed via fMRI adapted for the aforementioned tasks. This study in particular is currently in progress.

2.3. Neuroplasticity in Stroke Patients

Stroke is one of the most common causes of mortality worldwide. It occurs when blood flow is cut off from the brain, leading to numbness, difficulty speaking, and lack of coordination. Long term effects can include motor dysfunction, memory problems, and other cognitive impairments [32].

Flexor hypertonia of the wrist is a common condition in stroke patients [33]. Hand function, specifically in extension movement at the wrist and fingers is a strong indicator of post-stroke motor recovery [34]. In the pursuit of regaining motor function, therapies targeting hand function have been in development. However, conventional rehabilitation therapy is time consuming, labor intensive, and not all-encompassing.

In a study by Singh et al., a robotic hand exoskeleton was mounted onto patients with ischemic/hemorrhagic stroke. Mini-mental scale (MMS), Brunnstrom stage (BS), and the Modified Ashworth Scale (MAS) were used to determine the initial parameters of the patients. Patients were randomized simply using color cards. It was found that the robotic exoskeleton group showed significant improvement over conventional therapies in the modified Ashworth scale (MAS), active range of motion, and Fugl-Meyer scale. A significant increase in cortical-excitability in the robotic exoskeleton group over the control group was also observed. This was seen in a lower Resting Motor Threshold and increase in the amplitude of Motor Evoked Potential [12].

In another study, immersive virtual reality (VR)-based motor control training (VRT) was used to improve motor function in patients with stroke. Huang utilized serum biomarkers to better understand the effects of VRT on inflammation, oxidative stress, neuroplasticity, and upper limb motor function in stroke patients. Patients were randomized into either the VRT or conventional occupational therapy (COT) groups. Biomarkers including interleukin 6 (IL-6), intracellular adhesion molecule 1 (ICAM-1), heme oxygenase 1 (HO-1), 8-hydroxy-2-deoxyguanosine (8-OHdG), and brain-derived neurotrophic factor (BDNF) were assessed to acquire data on inflammation, oxidative stress, and neuroplasticity. It was found that there were significant improvements in the AROM-Elbow Extension ($p = 0.007$) and AROM-Forearm Pronation ($p = 0.048$). The study strongly supports the idea that commercial and immersive VR technologies should be applied in therapeutic treatment of chronic stroke [8].

3. Auditory Training

Learning in humans is largely mediated by sensory input. Of the primary forms of learning, which include sight, touch, and listening, auditory learning is the most related to linguistic ability. Reading, writing, and speaking in particular are heavily influenced by the ability to hear and distinguish sounds, especially at a young age. Being able to sense sound phrases and emotional tones is a strong indicator of language ability. Auditory neuroplastic training largely focuses on improving language skills. Current research favors utilizing auditory training methods as supplements for individuals with impaired language abilities. These impairments can arise as a result of injury to specific parts of the brain which govern language and speech, such as Broca's area and Wernicke's area [35].

3.1. Neuroplasticity in Music

Music has long been studied for its positive effects on auditory processing ability. Studies on listening to classical music and playing musical instruments have shown promising results. Neuroplasticity provides a stronger basis for the benefits of auditory training, especially in linguistic ability.

Musical training and music-based rehabilitation have been shown to enhance cognitive functioning and neuroplasticity. In one study, musical training was assessed in its clinical efficacy on traumatic brain injury (TBI). Neurological music therapy intervention was administered in either the first or last three months of a six-month follow-up period. The results showed that the intervention improved general executive function. Analysis of structural MRI data showed that gray matter volume increased in the right inferior frontal gyrus in both groups. All results were significant compared to the control period. These results suggested that music therapy, a form of auditory neuroplastic training, enhances executive function and leads to neuroanatomical changes in the prefrontal region [23].

4. Other Training

Some other forms of neuroplasticity training exist that do not fall under the above categories. These methods are more novel and nonstandard, including therapies relating to a pharmacological approach.

4.1. Magnetic Stimulation

Repetitive transcranial magnetic stimulation (rTMS) can modulate cortical excitability [14]. This could be beneficial in motor recovery following neurological injury such as TBI and stroke. However, rTMS is not well studied, and is an unconventional motor training method, which generally uses exercise or other physical methods.

Du et al. aimed to assess high and low frequency rTMS, hypothesizing that it would lead to motor skill improvement. Ischemic stroke patients with motor deficits were assigned to sessions of high frequency (HF) rTMS, low frequency (LF) rTMS, or a sham rTMS as a placebo. The primary outcome measurement utilized was a motor impairment score (Upper Extremity Fugl-Meyer). This was evaluated at baseline, after rTMS intervention, and after a 3-month follow-up. Cortical excitability and fMRI were also taken. Motor improvements were significantly larger in the two rTMS groups than the control group. The HF group showed increased cortical excitability in ipsilesional motor areas, while the LF group had decreased cortical excitability in contralesional motor areas. These areas were specifically targeted in the HF and LF rTMS [14].

4.2. Hyperbaric Oxygen Therapy

Neuroplasticity effects of hyperbaric oxygen therapy (HBOT) have been extensively studied in recent years. Evidence suggests that the combined action of hyperoxia and hyperbaric pressure leads to significant improvements in tissue oxygenation [24]. These combined interventions target both oxygen and pressure sensitive genes. Clinical studies have shown neuroplastic effects such as anti-inflammatory function, mitochondrial function restoration, induction of proliferation, and migration of stem cells. In one study, it was found that HBOT could combat pathogenesis of COVID-19.

Zilberman-Itskovich et al. utilized a randomized controlled trial to determine the effects of HBOT on COVID-19. Major cognitive impairments in post-COVID-19 condition are generally dysexecutive, or brain fog, which can impair psychology and functionality. The study saw psychiatric improvement associated with microstructure changes in the superior corona radiata area. It was also found that HBOT improved pain interference [24].

5. Conclusions

Neuroplastic training has shown great potential in combating symptoms of multiple neurological disorders and conditions. Physical training interventions have been shown to have positive effects on executive function, processing speed, and memory. Music therapy has been shown to impact neuroplasticity in a positive manner, improving linguistics and executive functions as well. Lastly, many novel training methods are still being developed, and the field is expanding to include more environment-based training methods. Studying neuroplasticity will grant us another aspect to our approach on neurological care and rehabilitation.

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