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Review Article

An Overview of the Therapeutic Effects of Environmental Enrichment on Traumatic Brain Injury

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ABSTRACT

Traumatic brain injury (TBI) occurs due to primary or secondary brain damages that result in temporary or permanent neurological deficits. The sum combined rates for TBI-related emergency department visits, hospitalizations, and deaths have escalated in 2001-2010. Environmental enrichment (EE) is a non-invasive therapy used to enhance learning and memory function. Given its positive effects on neuronal plasticity, EE can be applied as therapy for medical conditions such as neurodegenerative disorders (Parkinson's, Alzheimer disease) and TBI. This study reviewed the therapeutic effects of EE via music therapy and mastication for treatment of TBI. The introduction of EE in animal studies has been well established compared to human studies. This entails the use of various objects with different shapes, sizes, colors, textures, running wheels, ropes, plastic tunnels, balls, stairs, and shelters as part of this method that enhance physical activity compared with standard housing. Studies have shown that EE boosts cognitive function after TBI. It is also recommended to use wooden dowels as an EE tool in animal brain research.

Keywords: Environmental Enrichment; Traumatic Brain Injury; Therapeutic Effects; Music Therapy; Mastication; Neuronal Plasticity; Memory

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Introduction

Traumatic brain injury (TBI) is a neurological disorder resulting from injuries that lead to transient or irreversible neurological deficits (1). It may be caused by secondary consequences of primary injuries through direct external impact on the brain. The secondary consequences are characterized by molecular and inflammatory cascades of reaction that depolarize neurons, leading to structural brain damage (1). The condition has been consistently plaguing millions of individuals around the world annually, while the rates of TBI-related hospitalizations and mortalities were reported to have increased during 2001-2010 (1). However, in recent years, the number of TBI-related mortalities has decreased due to significant technological advancements in treatment regimens. This review highlights the significance of technological advancement in the treatment of TBI.

The progressive neurodegenerative nature of TBI often results in severe functional impairments in affected individuals, which may have serious public health-related consequences. Unfortunately, many of the available treatments for TBI are not effective and might cause adverse side events with usage (2). This has necessitated the need to develop more effective therapeutic means to prevent or reduce the progression of neurodegeneration as reported in TBI. Studies on animal models of TBI have shown the positive effects of environmental enrichment (EE), which helps in boosting activity of neurons, neuronal morphogenesis, and synaptogenesis (3). Environmental enrichment (EE) is a bionic technique used to enhance learning and memory function (4). Animals subjected to EE are likely to exhibit multiplication in dendritic spines, branching synaptic connections, and an increase in neural cell size. A microscopic view of the brain of rats subjected to EE showed an increase in the number of oligodendrocytes and astrocytes (5). However, the molecular mechanism by which EE boost the processes of memory and learning remains unknown (4).

ENVIRONMENTAL ENRICHMENT

It involves introducing sensory, cognitive (mental), and motor stimuli in a subject's environment (4). The neuroscientist by the name Donald Hebb made the earliest elucidation of EE in experimental animals, which entails free-roaming rats in a home environment compared to standard-house caged controls (6).

The prototype or archetype of EE in the laboratory entails keeping animal models in big cages permitting more space for the activation of cognitive, sensory, and motor function of the animals at a level higher than standard laboratory housing condition (4,7,8). Various objects with different shapes, sizes, colors, textures, and smells are available in the environmentally-enriched environment. Running wheels and ropes, plastic tunnels and balls, stairs, and shelters are part of this method that enhance physical activity (4,6,8). Environmental enrichment also entails social enrichment, which consists of keeping animals with several cage mates to vitalize complex social interactions that also stimulate sensorimotor and cognitive functions (6,7). Moreover, the sensory methods of enrichment which involve stimulation of visual, auditory, and olfactory sense are less explored (9).

The purpose of enrichment for strengthening animal well-being has been elucidated through the supply of sensory and motor invigoration using structures and resources that assist psychological wellbeing such as physical exercise, questioning of cognitive function, and manipulative events as regards species-specific features (5). The preliminary animal studies showed Environmental enrichment (EE) can bring extraordinary advantages at different levels of behavioral, anatomical and even (7).

An increase in the level's creativity has been surmised to vitalize memory and learning function. The helpful effect of EE has been corroborated in the specific area of the brain such as the hippocampus, and

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dentate gyrus cells, by boosting performance in behavior and synaptic plasticity in this area of the brain (3-5).

Traumatic brain injury

Traumatic brain injury occurs as a result of mechanical force on the head. It is a neurological disorder with diverse nature ranging from focal contusion (penetrating injury) to diffuse injury, single or repetitive concussion and mild TBI (10). Ischemia and hypoxia in brain tissues which leads to parenchymal softening with cell death are the key pathogenic features of TBI (11).

According to the report from the Centers for Disease Control (CDC), a total of 5.3 million Americans are living in the aftermath of TBI (10). Approximately, 1.7-2.0 million cases of TBI have been reported to occur every year in the United States. Between 2000 and 2016, 375,230 United State service members survived from TBI have divulged by the Armed Health Surveillance center (10). A report from the World Health Organization (WHO) also reported TBI as a principal cause of disability in 2020 (11). The severity of TBI can be examined using different methods but mainly through the Glasgow Coma Scale (GCS) score and the duration of the level of consciousness (LOC) or post-traumatic amnesia (PTA), and also clinical evaluation to assess the severity of the trauma. All grades of TBIs can be associated with long term physical, emotional, behavioral and cognitive complications affecting a person's ability to do normal activities (12). A GCS score of 3-8, 9-12, and 13-15 indicate severe, moderate, and mild TBI (10,12). Most (75-85%) TBI cases are mild and consisted of concussion, sub-concussion, and some blast injuries related to improvised explosive devices. Certain sports activities including boxing, American football, rugby, soccer, cheerleading, ice hockey, and wrestling, military service, physical abuse, and head banging can lead to mild TBI (10,12). Although people mostly experience total neurologic recovery after mild TBI, approximately 15-30% of individuals experience long-term neurocognitive and behavioral changes (12)

Part of the effect of injury in adult neurons mostly in the central nervous system (CNS) is because axon regeneration is obstructed due restriction by neuronal intrinsic elements and to external inhibitory factors in the environment (3). Cellular processes responsible for the regeneration of axons upon injury are modulated by activating the mammalian target of rapamycin (mTOR), which triggers the pro-survival phosphoinositide 3 kinase-AKT kinase pathway and promotes somatic and axonal protein synthesis. The Phosphatase and tensin homologue (PTEN) is an intrinsic inhibitor of mTOR signaling and studies indicated that crossing out of PTEN helps neuronal regeneration (13).

Classification of TBI

Traumatic brain injury is classified into focal or diffused classes depending on the presence of absence of focal lesions. Most injuries are mixed with both focal and diffuse elements. Examples of focal injury include contusion, subdural hematoma, epidural hematoma, and intraparenchymal hemorrhage, while diffuse injuries consist of axonal injury, hypoxic-ischemic injury, and microvascular injury that generally affect various anatomic regions. The main difference between critical focal injuries and severe diffuse injuries is their associated rate of mortality which is about 40% and 25%, respectively (12).

Overview of the therapeutic effects of EE at the molecular and behavioral levels

The therapeutic effect of EE has been revealed in p25 transgenic mice as it assists in the formation of new memories (spatial and fear conditioning), thereby making the mice recreate means to memories lost after neurodegeneration. Application of EE boosts visual cortical plasticity and reinforcement of memory via remodeling of the neurochemical variables of brain-derived neurotrophic factor, cholinergic, and glutamatergic systems (4). It also preserves

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the loss of neurons formation in the dentate gyrus (4,8). Environmental enrichment exerts neuroprotective effects against various toxins and genetically-induced models of neurological diseases by modulating predisposing factors and can ameliorate behavioral complications (14,15). Given its positive effects on neuronal plasticity, EE can be used for treatment of medical conditions such as neurodegenerative disorders (Parkinson's, Alzheimer disease), TBI, epilepsy, depression, schizophrenia, autism spectrum disorders, and stroke (6,8).

The exact mechanism of its neuroprotective action has been ambiguous but may entail the production of pro-regenerative neurotrophins or cytokines (3). The alleviating effect of EE has been corroborated in Alzheimer's disease (AD) as one of the most common neurodegenerative disorders. In a study carried out in AD11 animal model which expresses anti-nerve growth factor antibody and have neuro-degeneration in the hippocampus, EE resulted to a decrease in AD-like neurodegenerative features. Also, a remarkable depletion in amyloid deposits after the introduction of EE was seen in animal model of AD (4).

Overview of the therapeutic effects of EE at anatomical level

A previous study demonstrated rats nurtured in supersized cages with toys, ladders, tunnels, and running wheels had a higher level of cortical acetylcholinesterase and well-expand cerebral cortices in comparison to rats trained in standard cages (8).Furthermore, concerning the neuroplasticity of the adult brain, studies have revealed the multichannel EE-induced activation of neuronal plasticity that entails changes in the plasticity of neurons, protracted synaptic potentiation and depression, modification in gene transcription, and neurogenesis (8).

EE via mastication

The application of wooded dowels for mastication in animals such as rats and mice has shown to alleviate stress feedback and regulate hippocampal-dependent cognitive function (16). Furthermore, mastication palliates the stress-induced suppression of cell proliferation in the dentate gyrus that may underlie the affected function of the hippocampal formation with loss of the tooth (16). The adoption of hard pellet food instead of powdered food is imperative in experimental research as hard pellet food reverses the termination of neurogenesis in the forebrain subventricular zone that occur during the intake of soft food diet (16).

Underlying mechanism of action of EE

Physical activity in EE increases cerebral angiogenesis and circulation in the brain. In a study, three months of aerobic exercise increased neurogenesis and cerebral blood volume in the human hippocampus (16).

Environmental enrichment via music therapy

Music has been regarded as a curative/restorative treatment for the physical, emotional, and spiritual challenges of people. Music therapy can be classified active and receptive, which entails people composing music and people listening to composed music, respectively (17). The music intervention as a therapy for recovery in an individual with acquired brain injury may consist different interventions such as rhythmic auditory stimulation, electronic music-making, rhythmic-melodic voice training and listening to pre-recorded songs or live music. Music therapy has been discovered to reduce perturbation and boost the pace of orientation (17). Music also triggers physiological processes, enhances exercise, and rescinds pain perception. Flow in music is an effective propelling impetus for motor function (18). Music participation also reduces anxiety and stress and boosts feelings of pleasure and attentiveness by releasing neurochemicals by the brain. Biomedical speculations have revealed that music can stimulate neurophysiological processes and boost neuroplasticity (18,19).

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Some studies suggested that neuroplasticity can be induced via the act of learning novel complex motor task, for instance, music and juggling. It has been reported that juggling training causes neuroplastic changes within the first seven days, but no change occurs with ongoing training over months (20). However, sex differences may affect the neuroplastic magnitude as a result of sex hormone together with genetic effect. Furthermore, contrasts between males and females in the extent of neuroplasticity may include enhanced cortical excitability after anodal transcranial direct current stimulation and higher inhibition succeeding cathodal transcranial direct current stimulation in females (20). Besides, some of the results are antithetical and was presumed that sex interrelation with environmental factors in complex manners affects brain structure and function as confirmed in music training-induced neuroplasticity (20).

Furthermore, a common complication of traumatic brain injury is aphasia which leads to the loosing the capability for language production and comprehension (19).

Factors that determine the degree of language dysfunction are the location and level of the brain lesion. Lesion in the posterior superior temporal lobe (Wernicke's area) causes fluent aphasia, which implies that the patient shows connected speech with relatively typical expression duration, but speech may be incoherent to the listener with flaws in syntax and grammar. Lesion in the left frontal lobe (the left posterior inferior frontal) called Broca's area leads to nonfluent aphasia (19).

The introduction of melodic intonation therapy via clinical observation has been discovered helpful. It has two components: the intonation of words and simple phrases utilizing a melodic contour and the rhythmic tapping of the left-hand which go along with the production of each syllable which helps fluency (19).

The intonation unit was designed to affect the right hemisphere whose chief function is in processing spectral information and is better sympathetic than the left hemisphere to the slow temporal characteristics in acoustic signals (19). Singing and speaking take place in the frontotemporal cortices of both hemispheres, notwithstanding right hemisphere is highly activated when singing in contrast to speaking. The left-hand tapping unit of melodic intonation therapy works as a metronome/timekeeper/alarm clock, speed up auditory-motor mapping and attracts a sensorimotor network that regulates both hands and articulatory movements (19).

Introduction of EE to human model

The principal obstacle for translation of EE to the human population is the misunderstanding that EE in human settings is equivalent to an affluent lifestyle satisfied with luxurious adventures and merchandise (8). However, a curative technique that entails the recognition of brain-stimulating activities for a person or group, and structured programs consisting of enrichments in individual modus operandi. As it has been corroborated that mediation procedures entailing enriched cognitive inducement/vitalization physical activity, chewing gum, and music therapy are extremely efficacious in the therapy of neurological and psychological disorders (8,16,18).

CONCLUSION

Given the potential of EE in restoring hippocampal cognitive deficit, neuroplasticity, and oxidative stress, it is recommended to use EE via music therapy and mastication as a treatment for TBI and neurodegeneration. Furthermore, using wood dowels as part of environmental enrichment tool in animal brain injury showed a promising effect.

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Ethics approvals and consent to participate

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Conflict of interest

The authors declare that there is no conflict of interest regarding publication of this article

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