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Review Article

Neurologic Injury and Dementia: Update on Current Physiotherapeutic Intervention

Kevin Pierre[1], Alec Clark[2], Patrick Felisma[1], Sydney Weisman[3], and Brandon Lucke-Wold[1*]

[1]*Department of Neurosurgery, University of Florida, USA*
[2]*College of Medicine, University of Central Florida, USA*
[3]*College of Medicine, University of South Florida, USA*

***Corresponding author**

Brandon Lucke-Wold, Department of Neurosurgery, University of Florida, Gainesville, USA, email: Brandon.Lucke-Wold@neurosurgery.ufl.edu

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Abstract

Neurologic injury and dementia can lead to devastating outcomes for patients with extended course of disease. Secondary and tertiary injury can progress and lead to continued deficits and rapid neurodegeneration. In this review, we highlight alternative strategies that can target recovery for these patients and prevent further neurologic decline. We discuss the benefit of music therapy and acupuncture. We then look at transcranial magnetic stimulation and transcranial direct current stimulation. Finally, we look at the role of yoga and virtual reality. While several of these modalities are in their infancy, some have been used for generations. We argue for higher quality evidence to confirm effectiveness and clinical utility.

INTRODUCTION

Traumatic and non-traumatic neurologic injuries are associated with an extensive list of long-term neurologic deficits including dementia, executive functioning impairments, and motor deficits [1-5].Traumatic brain injury (TBI) and stroke are among the most common etiologies for neurologic injury [6,7].The nature and prevalence of cognitive decline after TBI has even necessitated the implementation of a distinct clinical disease entity: chronic traumatic encephalopathy [8]. This clinical term now encompasses the host of cognitive deficits that some patients experience chronically after TBI, especially repetitive TBIs, including memory deficits, behavioral changes, speech, and gait disturbances [9]. Studies have demonstrated the anatomical aftermath of TBI that can manifest as significant, progressive atrophy of deep brain structures, serving as a direct cause of the litany of chronic deficits seen in these patients [10]. Although these effects are most often manifested in patients who experience a moderate or severe TBI, patients that have experienced mild TBI, particularly those with repetitive mild TBIs, can experience these effects as well [11]. It is also important to note that functional outcomes post-TBI can continue to decline up to twenty years after the inciting neurologic injury and even serve as an independent risk factor for the development of other neurological diseases, including stroke and epilepsy.[12] Stroke is a very common non-traumatic form of neurologic injury that itself can cause both short-term and long-term deficits, including dementia and post-stroke aphasia [13-15]. Additionally, neurodegenerative diseases such as Huntington's, Parkinson's, and Alzheimer 's disease lead to progressive impairments. These patients develop difficulties with communication, expression, mood, motor function, and functionality. These multifaceted disease processes necessitate novel approaches to treat overall disease burden.

Conventional therapies, primarily pharmaceutical in nature, that are aimed at ameliorating post-neurologic injury cognitive impairment have generally had lackluster results [16]. Due to the prevalence of chronic cognitive impairment after these injuries, the lack of effective treatment has become a widespread clinical concern [17]. This has recently opened the door for the exploration of alternative treatment options and therapeutic adjuncts to help improve cognitive outcomes after neurologic injuries. The efficacy of many different types of alternative therapies, including music therapy, acupuncture, and repetitive transcranial magnetic stimulation, are increasingly investigated in these disease processes [18].

MUSIC THERAPY

The efficacy of music therapy in aiding neurologic recovery has gained traction as a viable clinical adjunct in recent years. A Cochrane Database review in 2010 first examined seven studies, including 184 participants, which found that rhythmic auditory stimulation (RAS) might be efficacious in improving motor and coordination outcomes of stroke patients who sustained prolonged neurologic deficits. Specifically, the review cited

improvements in gait velocity and symmetry, cadence, and stride length [19]. An update to this review was published in 2017, adding an additional 22 studies for a total of 29 studies (775 participants). This review reasserted the benefit on gait parameters and showed that music interventions can reduce post-stroke aphasia, enhance upper extremity function, and increase overall quality of life [20]. RAS has also shown promising impact on patients with idiopathic Parkinson's disease including improvement in gait parameters like gait velocity, cadence, stride length, swing time, and reduction in falls [21]. In patients with Huntington's, RAS suggests positive modulation of gait speed using rhythm cues via metronome [22]. In a study with 27 HD patients using RAS, results showed that training with rhyrhmic beat patterns led to higher unpaced gait [23].

A 2021 systematic review examined results from six studies and showed that music therapy increased motor outcome (stride length) and executive function in TBI patients [24]. Furthermore, Siponkoski et al., performed a crossover randomized controlled trial (RCT) in which 40 TBI patients were divided into two groups, one group to receive music therapy for the first 3-month interval of a 6-month period, and a second group to receive music therapy for the second 3-month period. Results from MRI data acquired from the subjects demonstrated enhanced volume of gray matter in the right inferior frontal gyri that occurred during the respective 3-month intervention period, as opposed to the control 3-month periods. In addition, these findings correlated with an increased ability to perform set-shifting tasks in patients in the intervention groups, a measure of executive functioning [25]. In addition to aiding in recovery of executive function in TBI patients, music therapy may also assist these patients in reducing levels of anxiety and depression and increasing capacity to regulate emotions [26].Thaut et al., tested the effect of vocal and instrumental warm-up exercises on measures of attention, executive function, emotional adjustment, and memory on 31 patients (80% of which were TBI patients) in a pre-test post-test quasi-experimental study [27]. Results indicated that patients undergoing this form of music therapy showed increased capacity for emotional regulation, and decreased levels of depression, anxiety, and sensation seeking behavior. Furthermore, there was significant improvement in mental flexibility on a standardized neuropsychological test measuring executive function, the Trail Making Test Part B [27,28].

Other measures of increased executive functioning capacity in TBI patients have been shown in other studies utilizing music therapy techniques. Formisano et al., used active improvised music therapy as a collaborative effort between the patient and the music therapist to assess the capacity for neurologic recovery in 34 patients who experienced severe brain injury. Results indicated a reduction in psychomotor agitation and improved psychomotor initiative, indicating the capacity for music therapy-assisted behavioral regulation enhancement [29]. A follow-up self-report questionnaire on Siponkoski's 2020 crossover RCT indicated that the TBI patients who received music therapy intervention in the first 3 months of the study scored higher on the Behavioral Regulation Index self-report than patients in the control group during the first 3 months. Thus, in addition to increased executive functioning in the patients who received music therapy intervention, higher levels of behavior regulation ability were also reported [30]. Although most studies on the effect of music therapy on TBI patients were performed on patients who sustained a moderate or severe TBI, a 2018 study used patients who sustained a mild TBI. This study examined 7 mild TBI patients with attention, memory, and/or social interaction deficits post-TBI. These patients were trained over the course of 8 weeks to play the piano, along with one control group of 11 healthy participants who also received piano training and one control group of 12 healthy participants who were not given piano training. Results from pre-test and post-test fMRI acquisition revealed increased markers of neuroplasticity in the orbitofrontal cortex in the mild TBI patients who received piano training compared to the control groups. Additionally, neuropsychological evaluation showed concurrent improvement of cognitive performance in the mild TBI patients, as well as enhanced sense of well-being and social interaction [31,32].

The effect of music therapy intervention on several parameters of neurologic recovery from stroke has been assessed by several studies. In 2008, Sarkamo et al., performed a single-blind RCT in which 60 middle cerebral artery (MCA) stroke patients were randomly assigned to a music group, a language group, or a control group for 2 months. In the music group, patients listened to music of their own choice daily for the duration of the 2 months, while the language group listened to audiobooks daily, and the control group did not listen to either. Results showed that patients assigned to the music group showed significant improvement over the language group and control group in verbal memory, focused attention, and decreased depression and confusion [29]. In a follow-up study by Sarkamo et al., in 2014, these results were extended to analysis of the gray matter volume using MRI data from stroke patients in each of the music, language, and control groups. Results demonstrated a larger enhancement of gray matter volume of the left and right superior frontal gyrus (SFG) and left ventral/subgenual anterior cingulate cortex (SACC) of patients in the music group compared to patients of the language and control groups in MRIs acquired 6 months after the commencement of the study. Further, the increases in SFG volume in music group patients were linked with the improvement of the verbal memory, focused attention, and language skills parameters, while increases in the SACC volume were linked with decreased depression and confusion levels [33]. Additionally, a study pooling data from two single-blind RCTs allocated 83 stroke patients to vocal music, instrumental music, or audiobook groups for 3 months post-stroke and measured the parameters of verbal memory, language, attention and mood using respective neuropsychological tests. Similar to the above studies, MRI data from stroke patients in each group was acquired 6 months post-stroke and compared. Results indicated that the stroke patients in the vocal music group scored higher in verbal memory tests over both the instrumental music and audiobook groups and scored higher in language recovery tests than patients in the audiobook group. MRI data showed increased gray matter volume in the left temporal areas of patients in the vocal music group compared to patients in the instrumental music or audiobook groups [34].

A 2019 systematic review including six RCTs with a total of 516 patients assessed the effect of five-element music, a type of music intervention employing five different melodies

relating to the five elements as dictated in traditional Chinese medicine practices, on the improvement of post-stroke aphasia [35,36]. Results indicated significantly higher language scores by post-stroke aphasia patients exposed to five-element music than either Western music therapy or no-music controls [36]. Interestingly, an RCT published by Haire et al., explored the effect of instrumental music therapy in conjunction with motor imagery on cognition, specifically the mental flexibility aspect of executive functioning. Thirty chronic post-stoke patients were randomly allocated to receive instrumental music therapy on its own or in conjunction with motor imagery and scores were assessed using the Trail Making Test Part B. Results indicated significant improvement in mental flexibility in the group of stroke patients that were given instrument music in conjunction with motor imagery [37].

Martinez-Molina et al., asserted that the neurorehabilitative effects of music therapy following neurologic injury may be a function of neural connectivity changes in the brain, particularly increased connection of networks between frontal and parietal regions [38]. Changes in neuroplasticity are hypothesized to be the underlying mechanism of neurorehabilitation in post-stroke patients, particularly as it relates to improving language outcomes when implemented in the early post-stroke stage of rehabilitation [39].

Studies evaluating quality of life as a primary outcome in HD patients remains scarce. One qualitative explorative study using focus groups identified areas in patient quality of life with parameters such as ability to communicate and express emotions, and family participation in care, are increased. With the significant decline in self-awareness, ability to speak, and prevalent behavioral problems, psychological aspects of the disease progression and the support of patient's loved ones are challenged. Music therapy studies have shown the potential for music to offer an avenue for communication and enhanced well-being. Therapy sessions can incorporate friends, patients, and family of patients, creating a supportive and inclusive environment [40].

Studies evaluating music therapy's effect on emotional function in PD patients have yielded promising insight. In a study of 16 PD patients participating in a systematic program of music therapy against 16 PD patients only participating in physical therapy, those undergoing MT showed significant improvements in emotional function. The study evaluated emotional state using the Happiness Measure, which included intensity and frequency of happiness. PD patients undergoing MT showed a significant difference in favor of music therapy compared to physical therapy regarding emotional functioning. The patients in MT also showed improvements in ADLs and quality of life. interpersonal interaction, support and increased sensory stimulation are theorized to explain the improved quality of life in these patients [41].

There has been increasing evidence on music's positive impact on AD patients' cognitive capacity. Simmons-Stern demonstrated that sung verbal information was better recognized than spoken verbal information in those with AD, suggesting that music increases arousal in those with HD [42]. Additionally, auditory-motor coupling has a profound effect on PD. An investigation of motor-sequence learning revealed that with non-verbal communication with music, AD patients performed significantly better when learning gestures in the presence of either a metronome or music [43].

A handful of studies have introduced the positive effects of MT on AD patients and psychomotor speed following a 6-month period of intervention. In one RCT daily activities incorporating music including singing and listening to familiar songs, dementia patients showed improved cognition, attention, executive function, and mood. As mentioned in prior discussion, caregivers' involvement and well-being is paramount to that of the patient. Singing showed to positively impact the emotional well-being of caretakers, while listening to music improved quality of life in dementia patients [44].

ACUPUNCTURE

The efficacy of acupuncture on functional recovery from TBI and stroke is less clear, but emerging studies are promising [45]. A 2011 systematic review including four RCTS with 294 total participants claimed that acupuncture may be effective in aiding neurologic recovery from TBI. However, conclusions are limited due to poor quality of studies cited and low participant number [46]. A systematic review on the efficacy of acupuncture following spinal injury suggested that acupuncture may have a positive impact on recovery of motor function but were similarly unable to report a definitive statement on the efficacy of acupuncture in this context due to poor quality studies and publication bias [47]. A more recent and comprehensive systematic review including 22 studies with 1644 total participants found that acupuncture of the back/front or head/back regions significantly enhanced motor function outcome and activities of daily living (ADL) in patients who sustained spinal cord injuries [48].

In 2017, Li et al., found that acupuncture significantly extended the amount of time that the post-TBI neuroprotective brain-derived neurotrophic factor (BDNF) and tropomyosin receptor kinase B (TrkB) remained elevated in TBI patients. Results indicated that these molecules remained elevated at significant levels for 2 days without acupuncture, which increased to 7 or more days with acupuncture treatment. Authors hypothesized that the acupuncture-induced prolongation of neuroprotective effects may cause an increase in neural plasticity post-TBI, enhancing recovery of motor, sensation, and cognitive parameters [49]. A 2019 RCT examined the effect of acupuncture on 70 TBI patients, with one group receiving pharmaceutical intervention alone and one group receiving pharmaceutical intervention in addition to acupuncture treatment. Results indicated that the acupuncture plus pharmaceutical intervention group had a significantly more profound recovery of ADL as indicated by increases in simplified Fugl-Meyer assessment and modified Barthel Index scales than the TBI patients in the pharmaceutical intervention only group. The authors also measured significantly higher BDNF and nerve growth factor (NGF) levels in the TBI patients in the acupuncture and pharmaceutical intervention group, hypothesizing that their anti-inflammatory effects were responsible for the significantly enhanced clinical improvement in this group [50].

In all, acupuncture therapy has been hypothesized to exert positive effects on recovery from neurologic insults through a

variety of mechanisms, including reduction of neuroinflammation, oxidative stress, and intracranial edema, as well as helping to facilitate regeneration of neurons and enhance corticospinal tract activity [51,52].

Acupuncture's role in AD is less certain due to the scarcity of evidence. The available literature focuses on animal models. Animal studies claim promising results in the application of acupuncture in AD mice, elevating BDNF levels and decreasing hippocampal amyloid B plaques. In a recent meta-analysis regarding acupuncture in the treatment of AD, Huang et al., suggests that acupuncture was significantly superior to medication in improving ADL scores, ADAS-cog scores, and MMSE scores. In a RCT with limited sample size performed by Jia et al. comparing donepezil with acupuncture treatment, significant differences were not reported in activities of daily living or behavioral symptoms [53,54]. More research is needed to evaluate the role of acupuncture in treatment for AD.

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

Several recent studies have evaluated the efficacy of repetitive transcranial magnetic stimulation on outcomes following neurologic injury [55]. Lee et al., conducted an RCT including 13 TBI patients that evaluated the effect of rTMS therapy on cognitive and mood outcomes. Participants were randomized into rTMS therapy and sham rTMS therapy groups and results were evaluated using standardized neuropsychological tests for depression (Montgomery-Asberg Depression Rating Scale) and for cognition (Trail making Test and Stroop Color Word Test) two weeks after commencement of the trial. Results showed significant improvement in scores of all three standardized tests for the rTMS group compared to the sham group, indicating enhanced effect of rTMS on both depression and cognition [55]. Zhou et al., found improvements in several measures of cognitive impairment, including GCS score and modified Barthel index score, in TBI patients who received rTMS in addition to cognitive training compared with TBI patients who received only cognitive training [56]. A 2021 systematic review examining 7 studies found that rTMS only had a significant anti-depressant effect on TBI patients in the short-term period as the anti-depressant effects had completely worn off by 1-month post-TBI. rTMS was also found to have a significant effect on improving visuospatial memory in these patients [57].

Several studies have however demonstrated results suggesting that rTMS therapy may not be effective for cognitive neurorehabilitation efforts in these patients. In a 2020 RCT, Rodrigues et al., showed no improvement in anxiety outcomes for 36 moderate or severe TBI patients who received rTMS compared to those who received sham rTMS. However, they did note statistically significant improvements in both depression and executive function, even up to 90 days post-study [58]. An RCT published by Rao et al. examined the effect of rTMS on 30 TBI patients suffering from depression and concurrent neuropsychiatric symptoms, including suicidality and anxiety. Results indicated minimal improvement in depression and neuropsychiatric symptoms even after rTMS intervention [59]. Mitchell et al., performed a systematic review including five studies that evaluated the effect of rTMS therapy on neurologic injury-induced dysarthria. Results indicated limited evidence to suggest that rTMS has a positive effect on recovery from dysarthria in this context [60]. Furthermore, a randomized, double-blind, placebo-controlled trial in 2019 found no significant differences in cognitive function outcomes in 30 chronic post-diffuse axonal injury (DAI) patients who received rTMS therapy [61].

There is limited data in rTMS therapy in AD patients. Studies applying rTMS to the dorsolateral prefrontal cortex (DLPFC) and evaluating naming and language performance showed improvements in action naming in mild AD patients according to MMSE. In those with moderate to severe AD, both action and object naming were found to be improved following bilateral DLPFC rTMS. These studies report no known side effects [62].

In all, rTMS may be effective for recovery from neurologic injury for a limited number of symptoms, including alleviation of depression and some measures of cognitive impairment [63]. However, results thus far have been mixed and, if present, any true positive effects may be limited to the short-term.

TRANSCRANIAL DIRECT CURRENT STIMULATION

A few studies have hypothesized a positive effect of transcranial direct current stimulation (tDCS) on improving motor outcomes [64-66]. A 2020 meta-analysis examining 67 studies (1729 participants) examined several neurologic outcomes in post-stroke patients who received transcranial direct current stimulation (tDCS). Authors found very low-to-moderate evidence of tDCS increasing ADL ability of post-stroke patients and very low evidence for efficacy on improving hemispatial neglect. Furthermore, authors asserted that there is likely no significant effect on motor outcomes or other cognitive impairments in stroke patients who receive tDCS compared to those who do not [67]. A 2019 systematic review suggested that tDCS may be more effective in increasing positive cognitive and motor outcomes if used as an adjunct to other alternative therapies [68].Thus, the current evidence of tDCS, particularly as a monotherapy, as being an effective treatment modality in this context is currently lacking.

Following suit in terms of rTMS evaluation, tDCS studies are scarce as well. According to a systematic review performed by Freitas et al. two studies evaluated the role of tDCS in AD. The first evaluated improvement in recognition memory in AD patients, finding specific progress in accuracy of word recognition following anodal tDCS applied to the temporoparietal region. The second study found that improved visual recognition memory resulted following anodal tDCS to the left DLPFC and left temporal cortex. There was no impact on working memory, although this was expected [62].

YOGA

There is currently little evidence on the efficacy of yoga on improving cognitive outcomes from traumatic and non-traumatic disease processes compromising neurologic function [69,70]. A 2017 systematic review including two RCTs showed very low evidence for the impact of yoga on improving memory and anxiety outcomes based on a low total number of 72 pooled stroke participants. Authors noted no difference in depression

levels or physical, communication, or stroke recovery outcomes in stroke patients who participated in yoga compared to those who did not [71]. A more recent systematic review published in 2020 included six studies comprised of participants with acquired brain injuries. For patients with acquired brain injury, yoga was found to assist in psychological and physical adjustment, improve respiratory function, and improve quality of life. For stroke patients specifically, improvements in memory and motor functioning and quality of life measures were observed in those participating in yoga [72]. A small study including seven patients with chronic brain injury examined the effect of eight total weeks of yoga training. Results indicated statistically significant improvements in mobility and balance from pre-study baseline to post-study [73]. Krese et al., also demonstrated that TBI patients who participated in yoga sessions may also have improved sleep and sleep hygiene [74]. In all, yoga may aid in increasing these patient's self-perceived quality of life and motor function outcomes, although results so far are not convincing.

The role of yoga in treatment of AD has conflicting evidence with respect to improvement in common variables such as depression, cognitive function, memory, and physical ability. One study did not note any significant changes in measured parameters, while another study found significant improvement in balance. The latter study did not see significant changes in the Six-Minute Walk Test or the Gait Speed Test, variables related to physical ability. These studies lack both a control group and a reliable sample size, and future evaluations are recommended to seek increased participants and implement use of control participants [75,76].

VIRTUAL REALITY

Virtual reality is an up-and-coming technology whose clinical applications are being explored in many disease processes, including Parkinson's disease [77-79]. Little is known of the effect of virtual reality intervention on patients recovering from neurological injury. A 2018 literature review including 11 studies on the effect of virtual reality training on recovery of TBI patients found that virtual reality training may have some positive effect on gait or cognitive effects. However, it is not possible to draw conclusions due to the scarcity of high-quality studies [80]. A systematic review in 2019 reviewing nine studies on the use of virtual reality training on cognitive rehabilitation of TBI demonstrated improvement in executive function, attention, and memory in these patients after virtual reality training [81]. In 2021, an RCT published by Choi et al. examined 80 pediatric patients with brain injury suffering from a wide range of neurological deficits who were given either conventional occupational therapy alone or a combination of virtual reality intervention and occupational therapy. Results from this study indicated that children in the virtual reality group demonstrated significant improvement in their ability to independently perform ADLs and in motor functions including upper extremity dexterity and active forearm supination [82].Thus, virtual reality has shown some preliminary promise in both pediatric and adult populations in improving motor and cognitive outcomes from several neurologic disease states.

A case study performed by White and Moussavi evaluated whether a virtual reality navigation task over 7 weeks could promote conservation or improvement of spatial cognition in an AD patient with mild cognitive impairment. The patient showed improved spatial navigation over the course of the study. Subjective improvements per the subject's significant other were mentioned including mood, orientation while driving, and daily functioning. More studies evaluating the use of virtual reality are encouraged [83].

CONCLUSION

In summary, there is emerging evidence on the use of physiotherapeutic intervention in neurologic injury. We call for further high-quality studies investigating these treatment modalities to improve outcomes for patients with these conditions.

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