Neurological Sciences and Neurosurgery

Short Communication

DOI: https://doi.org/10.47275/2692-093X-138
Volume 5 Issue 1

A Digital Therapeutic Approach in Neurology

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Abstract

In digital health, digital therapeutics (DTx) refers to delivering evidence-based therapeutic interventions to patients that are driven by software to prevent, manage, or treat a medical condition. Medications, devices, and other therapies may be used independently or in conjunction with them to optimize patient care and health outcomes. DTx has great potential to improve outcomes for chronic disabling diseases. A narrative review of DTx in the management of neurological disorders is presented in this article.

Keywords: Digital therapeutics tools; Digital therapeutics; Neurological symptoms; Neurological disorders; Rehabilitation

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Citation: Kataveni S, Thota Y (2024) A Digital Therapeutic Approach in Neurology. Neurol Sci Neurosurg, Volume 5 Issue 1. DOI: https://doi.org/10.47275/2692-093X-138

Received: March 04, 2024; **Accepted:** June 13, 2024; **Published:** June 17, 2024

Introduction

DTx initially aims to help prediabetics lose weight and exercise more to avoid getting sick. As defined by the American Psychological Association, DTx refers to a method of treating a medical or psychological condition using digital and online health technologies. In addition to smartphone apps, wearable devices (tracking sensors), web-based studies, social networks, behavioral science, and telemedicine platforms, these are technology-based solutions which allow patients and their social interaction to be monitored and intervened upon when necessary. Table 1 illustrates the differences between wellness tracking applications and digital supplements [1-3].

EHealth defines digital health as "the use of information and communications technology to improve health and health-related fields." Health technology describes any system, platform, or technology that engages consumers for lifestyle, wellness, and health-related purposes; captures, stores, or transmits health data; or supports life science and clinical operations. The Digital Therapeutics Alliance defines DTx as the delivery of evidence-based therapeutic interventions to patients driven by software in order to treat, prevent, or manage a medical condition. In order to optimize patient care and health outcomes, they are used independently or in conjunction with medications, devices, or other therapies [4, 5]. By using DTx, conventional clinical practice could be overcome, costs associated with attending hospitals and doctors' clinics could be reduced, healthy lifestyle behaviors could be improved, medications could be continuously monitored, administrative tasks and routine communication could be optimized, and administrative tasks and routine communication could be reduced. A DTx treatment could therefore be very beneficial for chronic disabling diseases [6].

Smartphones, tablets, computers, and videogame platforms can be used as DTx tools to improve therapy management and rehabilitation by combining screen devices with software algorithms. DTx is an important treatment option for patients with neurological dysfunction, and this review provides an overview of how it can be used [7, 8].

Methods

By combining screen devices with software algorithms,

Table 1: Difference between DTx and wellness tracking applications [3].

Category	DTx	Wellness tracking applications
Indication	Focused on one condition mostly	Focused on various condition
Prerequisite	Regulatory requirement like multicenteric randomized controlled trials among target population	Minimal technical requirement for downloading from application store
Therapeutic claim	Safe and proven therapeutic value by collection and analysis of real-world evidence	Unsubstantiated claims about clinical benefits
Mode of access	Business to business-to-consumer	Business-to-consumer
Key performance indicators	Compliance	Number of users
	Prevention of readmission or	Usage
	Repeat intervention in a given amount of time	Direct turnover
Reimbursement claim	It can be reimbursed by payers depending on DTx compliance	It can only be subscribed by consumers.

smartphones, tablets, computers, and videogame platforms can be used as DTx tools to improve therapy management and rehabilitation [9]. DTx is an important treatment option for patients with neurological dysfunction, and this review provides an overview of how it can be used.

Sensorimotor Functions

Despite intact sensory functions, motor rehabilitation cannot be achieved without accurate and adaptable visual and proprioceptive inputs. Enhanced sensory stimulation is achieved with iPads, smartphones, and virtual reality software [10, 11].

Patients with upper extremity motor impairment, balance disorders, and gait dysfunction may benefit from virtual reality-based interventions. Virtual reality-interventions have shown to be highly effective for upper and lower limb motor training in recent years in several randomized controlled trials. The use of virtual reality techniques allows interaction between virtual objects and motion in a variety of virtual environments [12]. For post-stroke upper limb rehabilitation, the "Computer-Assisted Rehabilitation Environment" (CAREN) is an interactive motion-based technology. The effectiveness of CAREN was compared to the effectiveness of traditional physical exercise training in a randomized controlled trial. Using three-dimensional visual cues, the training simulates a supermarket shopping scene, engaging the patient in reach to grasp activities. The task was performed in a sitting position to maximize shoulder and elbow range of motion. Both groups trained for four weeks, three days per week, for 45 min. There was a significant improvement in arm motor impairment measures, clinical impairment scores, and activity levels in the intervention group as compared to the control group after the training [13]. In some cases, there were only small differences between groups. The absence of a significant clinical difference between the two groups does not allow us to conclude that CAREN is superior to traditional interventions despite significant changes on the Reaching Performance Scale for Stroke and elbow subscale [14]. As such, digital interventions may be useful in cases where traditional approaches are not feasible (i.e., pandemics, for the underserved, etc.) or in conjunction with traditional therapies.

"Leap Motion Controller" is an optical hand-tracking module that allows for submillimeter accuracy in tracking hand movements without wearing wearable devices or sensors. The system generates a virtual image of the upper limbs on a screen, and patients are directed to perform the suggested functional task in accordance with it [15].

Proprioception is rarely studied in rehabilitation systems. The use of rhythmic active motion, angle repositioning, and standing on an air cushion with support has been suggested as a way to improve proprioception. Using virtual reality technology, Kim et al. [10] developed a new type of rehabilitation system to train stroke patients' proprioception. It relies solely on proprioception feedback to move the arm to the target position [16]. The proprioception of stroke patients could be adjusted by repeating this procedure. A study showed that stroke patients were able to improve their motor control with virtual reality proprioception feedback training.

Balance problems can also be managed using virtual reality as an alternative to traditional rehabilitation therapies. A training program using the "CAREN" was evaluated by Kalron et al. [11] for improving balance in patients with multiple sclerosis (MS). Three hundred and thirty-two patients with MS participated in a randomized controlled trial [17]. A balance training program was provided to each group twice a week for six weeks, lasting for thirty minutes each time. Tests of clinical balance and posturography show improvement in both groups. Virtual reality-based DTx also increased the functional reach test score and fear of falling score of the group that used DTx compared to the control group.

Clinical studies have also examined videogame-based rehabilitation programs for patients with neurological diseases. DTx-based virtual reality devices could be used to play exercise games, regardless of their primary purpose [18]. In addition to motor dysfunctions of the upper and lower limbs, they could also address balance impairments. It is a Microsoft-Kinect-based virtual reality software program that provides motor rehabilitation in the English language called Jintronix Rehabilitation System (JRS WAVE). With fun and engaging video games that can be played at home or in an outpatient setting, you can improve upper limb function, standing balance, and gait. Subjects in the intervention group used the device for 1 h/week for 8 weeks in the randomized controlled trial comparing virtual reality-based training with standard physiotherapy. A significant difference was not found between the intervention and control groups in terms of standing balance (primary outcome). As a complement or alternative to traditional rehabilitation tools, exergames could be a useful tool [2, 19].

As compared with no intervention, authors like Yazgan et al. [15] investigated the effects of exercise training with two different exergaming systems on balance, functionality, fatigue, and quality of life in patients with MS. Physiotherapists supervised the exercise program in the intervention group two days a week for eight weeks. "Nintendo Wii Fit" and "Balance Trainer" training improved balance, function, and quality of life, and reduced fatigue severity [20].

According to Ozdogar et al. [19], a recent randomized controlled trial investigated the effects of video-based exergaming training on upper extremities, cognitive function, and other MS-related symptoms in patients with MS. There were three groups of sixty patients: those who received video-based exergaming, those who received conventional rehabilitation, and those who were not [21]. For eight weeks, therapy sessions were held once a week for the intervention groups. According to the study, video-based exergaming has almost as much effect as conventional rehabilitation in terms of improving walking, upper and lower limb functions, cognitive functions, fatigue, and depression.

A blinded, parallel-group randomized controlled trial of the "Interactive Rehabilitation Exercise Software" was conducted in an inpatient stroke rehabilitation unit to address coordination and balance impairments. Virtual reality games (such as soccer goaltending, snowboarding) were played by participants in the treatment group standing up, which challenged their balance and weight shifting. Individuals in the control group, on the other hand, sat and played games that did not require them to shift their weight. Additional to their regular inpatient rehabilitation therapy sessions, participants in both groups completed 10 - 12 sessions of 20-min interactive virtual reality exercises [22]. A Timed Up and Go test was used as the primary outcome measure. Additionally, the Two-Minute Walking Test and the Chedoke McMaster Stroke Assessment Scale Leg domain were assessed as secondary outcome measures.

After the final training session for the Timed Up and Go test and the Two-Minute Walking Test, both groups met minimal clinically important difference values. The treatment group showed greater improvement on the Chedoke McMaster Stroke Assessment Scale Leg domain than the control group after the final training session [23]. Due to the overlap in the confidence limits, this study's findings should be read with caution, since virtual reality exercises might have positive effects on stroke rehabilitation inpatients.

In order to target balance impairments, eTraining is an Internet-based home training program. "eTraining" was compared to hippotherapy in a randomized controlled trial. For 12 weeks, patients with MS received hippotherapy or Internet-based home training. Both intervention programs improved static and dynamic balance similarly [24]. In addition, Internet-delivered behavioral interventions and Web-based physiotherapy exercises have been used to promote physical activity at home.

Cognitive Functions

Neuroplasticity in the brain can be enhanced through cognitive rehabilitation through digital devices. The online platform "Cogmed" provides therapeutic training to improve working memory. Compared to a control group, the intervention group significantly improved working memory and executive functions with Cogmed in two randomized controlled studies. In "Constant Therapy," patients with speech, language, and cognitive deficits caused by strokes, brain trauma, and other neurological diseases can rehabilitate themselves using an iPad application. Tasks are provided to train speech and memory. A clinical trial compared the "Constant Therapy" intervention with a traditional approach. In addition to 1-h clinic sessions with a clinician, patients in the intervention group also received "Constant Therapy" at home once a week for 10 weeks. Patients who used "Constant Therapy" improved their memory tasks compared to those who did not, showing that tablet-based software can be used to deliver tailored speech and cognitive therapy. Compared to computer-based platforms and iPad applications, virtual reality-based cognitive training has been less studied in clinical studies. Compared to subjects undergoing standard cognitive rehabilitation, subjects using virtual reality-based devices demonstrated greater improvements in attention and memory skills [25]. It is not possible to generalize the findings from the small sample size (6 patients per group) and the short follow-up period to all stroke patients, however.

In the case of fluent aphasia, semantic training is provided, while in the case of non-fluent aphasia, phonological training is provided. A variety of tools are available for semantic and phonological training, including computer-based interventions, tablet-based interventions, and virtual reality-based interventions. Aphasia rehabilitation usually involves both types of training in combination. Stroke patients can use "StepByStep" and "Multicue" to find words with the assistance of computers. Patients undergoing the training showed a significant improvement in naming abilities in two randomized controlled trials [26].

The "Cognitive Training Kit" (COGNI-TRAcK) is a software application that allows the user to self-administer a customized cognitive training program at home. Working memory exercises are used in this program. The first study used the app to administer an 8-week at-home intervention to 16 patients with MS and cognitive impairment. The intervention consisted of five 30-min sessions per week for eight weeks. Usability, motivation, and acceptance of the application were all rated highly. Adaptive versus nonadaptive cognitive training was compared in a study of twenty-eight patients with MS. It is concluded that "Cognitive Training Kit" is an effective tool for cognitive rehabilitation in MS patients, but only when used in conjunction with an adaptive working load [27, 28]. A recent pilot study assessed the effectiveness of an in-home, tablet-based digital treatment for improving processing speed in adults with MS compared to a control word game. Processing speed was significantly improved by both interventions. The post-treatment observation period showed that 72% of participants who received the in-home digital intervention maintained a clinically meaningful improvement in processing speed, compared to 37% of participants who received the active placebo control. According to the authors, digital intervention resulted in substantial and durable improvement in processing speed.

The performance of cognitive functions has also been shown to be enhanced by motor exercise games. A variety of cognitive and motor functions can be positively influenced by exercise games, such as memory, attention, and visuospatial skills [29, 30].

MINWii (on Nintendo R Wii™) is a serious game for administering active music therapy in which the player plays a well-known song on a virtual keyboard as part of active music therapy. Few serious games (games designed for a primary purpose other than pure entertainment) have been developed specifically targeting patients with Alzheimer disease. Video games and music therapy are used in this Renarcissization-based approach. Patients who have gradually become despised by their caregivers are re-encouraged through renarcissization. Patients are able to enhance residual abilities and engage with this approach [31]. Behavioral symptoms, which are a major cause of institutionalization, are reduced by improving patients' self-images (Renarcissism).

A cooking tablet game, Kitchen and Cooking, requires the player to select ingredients from the kitchen, plan actions, and finally execute specific gestures to complete each action. Aside from training executive functions, the app also includes activities to train attention, object recognition, and praxis. On the basis of self-report questionnaires assessing the overall game experience of 21 patients (9 with mild cognitive impairment and 12 with Alzheimer's disease), this serious game was accepted by most patients, suggesting its effectiveness for assessing and stimulating executive functions (such as planning ability) and praxis, even in patients who are apathetic [32].

It is a web-based application that trains memory, attention, and mental flexibility. In a randomized controlled trial, 46 patients with neurocognitive disorders (32 with probable Alzheimer's disease and 14 with mixed disorders) were evaluated for its effects on cognitive and behavioral symptoms. A 12-week study (four sessions per week) compared patients who used "MeMo" and those who did not use it. Over a 3-month training period, attention and apathy showed a small but significant improvement [33-35]. Regular use of the app, however, was necessary to observe these positive effects on attention and motivation.

Cognitive and Motor Interactions

However, there may be some possible interpretations, either at a cellular or behavioral level, for the effects of physical exercise on cognition. Throughout all stages of life, mammalian brains exhibit persistent plasticity at the cellular level. Learning new skills, consolidating, and retrieving memories, and reorganizing neuronal networks are all enabled by neuronal plasticity. Behaviorally, tasks may become automatic with practice and less demanding as they become less attention demanding. It may also be possible to develop less attention demanding strategies through continuous physical training. Aerobic exercise improves performance on tasks involving executive control of attention [36]. Further, cardiovascular fitness may enhance neural processing efficiency or increase metabolic resources available for task performance.

It may therefore be more effective to combine cognitive treatment and physical training to induce stable improvements in cognitive functions in healthy elderly adults than to focus on just one domain. Studies suggest that physical activity and structured exercise improve cognitive functions, with executive functions showing the most consistent improvements. The potential for cognitive rehabilitation is great when video games require physical movement while a patient conducts cognitive exercises [37]. In "X-Torp" (on Microsoft R Kinect), the player controls a submarine using stationary movements of the lower limbs in real-time while using the Kinect. There are short missions following a story plot that require players to destroy other ships at sea. The "X-Torp" was shown to improve cognitive function and physical activity in a clinical study. Although they may be effective in neurological rehabilitation, games with violent content should be used with caution. It has been found that violent video games reduce child-to-parent violence rates, but longitudinal studies have not found any substantive links between aggressive game content and youth aggression [38].

Due to the transfer effect between motor and cognitive skills, combining motor and cognitive training could be beneficial. DTx based on virtual reality has increasingly been used for the rehabilitation of Parkinson's disease patients. An analysis of more than a thousand participants explored the efficacy of virtual reality-based training. Virtual reality training improves cognitive function, motor function, balance, coordination, and quality of life in Parkinson's disease patients. Parkinson's disease rehabilitation has been made possible with the use of exercise games, which require the user to perform physical movements while performing cognitive exercises [39]. Several randomized controlled trials have been conducted in the last 10 years, and most of them utilized the "Microsoft Kinect" and the "Wii Balance Board" for Parkinson's disease rehabilitation. According to Garcia-Agundez et al. [12], exercise-based rehabilitation is feasible, effective, and safe in patients with Parkinson's disease.

The mechanisms underlying physical exercise's effects on cognition are still not fully understood; however, it is assumed that the prefrontal cortex plays a significant role in motor exercise performance. The efficiency of neural processes related to cognitive functions may also be enhanced by physical training, according to hypotheses.

Presence of Other Neurological Symptoms

DTx could also help with other neurological symptoms associated with neurological disorders (visual dysfunction, speech impairment, dysphagia, fatigue, depression, and pain) [40].

Visual field impairment

A few studies have explored the feasibility and effectiveness of the developed DTx for treating visual field defects after stroke. Traditionally, rehabilitation for visual field defects takes a different approach: compensation therapy emphasizes the preservation of residual abilities; restitution therapy emphasizes the regeneration of neural plasticity by presenting repetitive light stimuli in a border zone between the blind field and the spared field. Computer-based compensatory therapies such as "NeuroEyeCoach" and "VISIOcoach" have been proven effective in treating patients with visual field defects [41].

Fatigue

In order to help patients with MS manage their fatigue, a mobile health solution called "More Stamina" was designed and developed using a user-centered design and evidence-based process. "More Stamina" is currently being tested for feasibility, acceptability, and usability. With this tool, people with MS can organize tasks in a gamified fashion to manage their energy and minimize the effect of fatigue on their daily lives. Users can input their daily goals into the tool as a to-do list [42].

Depression

Patients' quality of life can also be improved with an appropriate treatment for depression, another common symptom.

Depression can be managed with DTx by using "Deprexis." Cognitive-behavioral therapy is combined with mobile technology and dialog therapy in this web-based self-help program. MS patients with depression were enrolled in a randomized controlled trial to examine its efficacy. Randomization was conducted between the intervention group and the control group (waiting list). According to the study findings, patients with MS who underwent web-based depression intervention programs showed an improvement on the Beck Depression Inventory, while those in the control group showed a worsening [43].

Pain

There is also evidence that virtual reality reduces pain intensity and discomfort in patients suffering from a variety of chronic pains; it is an intervention based on a distraction technique since it diverts the patient's attention from their mental processing, thereby reducing the amount of pain they are aware of.

A recent study compared the effectiveness of a 3D head-mounted virtual reality device to 2D screen devices in reducing neuropathic pain in people with spinal cord injuries. In a single-session randomized cross-over trial, 16 men with established spinal cord injury and chronic neuropathic pain participated [44]. Compared to 2D screen applications, participants reported significantly lower pain intensity following immersive virtual reality intervention, suggesting that immersive virtual reality could complement current pharmacotherapy.

Managing Self-care and Adhering to Therapy

Medical adherence could be increased, healthy lifestyles could be maintained, access to care could be improved, and costs could be decreased through DTx interventions.

Healthcare systems continue to face unmet needs related to stroke patients' adherence to medical therapy. In order to prevent secondary strokes, the "FARMALARM" application for smartphones is available in the Spanish language. In addition to monitoring his physical activity, recording, and sharing vital parameters with the physician as well as monitoring therapy adherence, the patient can also receive advice about a healthy lifestyle. The app provided visual and audible alerts that were useful for secondary stroke prevention, improving medication adherence, and maintaining healthy behaviors. Compared to patients who did not follow the "FARMALARM" program, those who followed it had a higher rate of total control of critical vascular risk factors [45-49]. Using a digital platform and a personal coach, a digital self-management program was developed in a pilot study to monitor vascular risk factors after stroke. Through the platform, patients were able to record cardiovascular risk profiles. Stroke coaches are alerted if the patients' values exceed the defined threshold. In the intervention group, the vascular risk was significantly reduced at 6 months compared with baseline scores on the "Systematic Coronary Risk Evaluation: High and Low Cardiovascular Risk Charts."

"MS Dialog" is a web- and mobile-based software application that records patient data about subcutaneous interferon beta-1a administration, clinical outcomes, and patient-reported outcomes. "MS Dialog" was found to be easy to use and superior to patients' previous methods for improving self-management of their condition in a study exploring its usability among patients and clinicians. "BETACONNECT" is a digital tool that makes managing MS therapy more structured. Monitoring disease-modifying therapies can be accomplished with the "BETACONNECT" system. Patient self-management and communication between healthcare providers and patients are supported by this system, which combines auto-injector technology with digital tools. A nurse and physician can access a platform and an injector through the system. With the app, users can manage their own IFN-β-1b therapy. A rotation scheme for injection sites is included as well as injection planning and recording. When it's time for the next injection, patients can be notified by email or push message. Nurses and physicians caring for patients with MS can share injection data to facilitate communication. A unique benefit of the "BETACONNECT" is that it automatically records every injection, allowing an unbiased evaluation of compliance [50-53]. Smartphone reminders did not significantly improve medication possession rates of disease-modifying therapies in a study exploring the usefulness and validity of smartphone-based e-diaries to promote therapy adherence in MS patients.

People with epilepsy still have unmet needs in terms of satisfactory seizure control and optimal medical compliance. It was the "WebEase" platform that delivered self-management content for the first time. Patients with epilepsy could complete three modules online (medication adherence, sleep, and stress). An intervention group compared to a control group showed improved adherence, self-management, and stress reduction using the platform. An intervention based on a smartphone app was also evaluated in a recent clinical trial on 327 adult epilepsy patients. It was important for participants to achieve seizure control and optimal quality of life by improving their therapeutic compliance and lifestyle. In addition to a medication calendar and educational forum, the app provided patients with a facility for reporting seizures and requesting consultations online. Epilepsy-specific apps are proven to improve patient self-management and reduce seizure frequency in the study [54-57].

Additionally, cognitive therapy, psychosocial interventions, and educational interventions reduced epileptic seizures. Epicadance is an epilepsy mobile app that integrates all these therapeutic modalities including epilepsy self-care, behavioral interventions, medication reminders, and anti-seizure music, including Mozart's sonata K.448.

In the recent trial, another digital solution was explored for improving self-care and treatment adherence. A "Parkinson Tracker App" was downloaded by patients in the intervention group and conventional treatments were administered to those in the control group. In addition to sleep, exercise, a balanced diet, mood, energy, medication, and movement, the app also collected data on self-monitoring measures. "Parkinson Tracker App" significantly improved self-reported medication adherence and patients' perception of the quality of clinical consultations compared to conventional treatment [58, 59].

Wearable sensors such as accelerometers or electromyography recordings can detect motor seizures in people with epilepsy. With high sensitivity (90%) and low false alarm rates (0.1/day), "Epi-Care free" records generalized tonic-clonic seizures similarly to epilepsy monitoring units [60-62].

It can also be used as a touchpad or a storage and transfer system for health information at home (temporary or permanent tattoos). The use of tools-based devices to monitor electroencephalogram can help overcome limitations related to monitoring electroencephalogram in a lab or clinic, since they can record brain signals for a long time while people are away from the laboratory and moving around. Transthoracic impedance measurements were also used to monitor real-time respiration using unperceivable temporary tattoo electrodes. With this technology, electromyography and electrocardiogram signals, as well as respiration, can be monitored in real time.

Conclusion

Many neurological dysfunctions can be supported by the application of DTx, according to the available research. The following issues remain unresolved: the economic impact on the healthcare system, the limited validation of the digital devices in non-English languages, the lack of standardized intervention protocols. Furthermore, underserved populations may not have access to high-speed broadband in less developed areas. There is no consensus regarding the outcome measures, the training duration/intensity, and the types of exercise games used to assess the clinical effectiveness of tele-rehabilitation using virtual reality and video games.

Current regulations and reimbursement guidelines are preventing the implementation of DTx in clinical practice. Promoting the use of DTx in clinical practice requires understanding and overcoming barriers to effective regulation and reimbursement. In order to promote the use of reimbursed DTx devices in clinical settings, future studies are needed to identify the most effective intervention protocols, efficacy, safety, feasibility, and benefit-cost ratio.

From the COVID-19 pandemic, we have learned that telemedicine and digital devices can not only provide remote consultations but also simultaneously transmit images and communicate information, which greatly reduces pressure on frontline staff. DTx services should be promoted not only in epidemic conditions, but also in routine care in the future.

Acknowledgements

None.

Conflict of Interest

None.

References

1. Yekutiel M, Guttman E (1993) A controlled trial of the retraining of the sensory function of the hand in stroke patients. J Neurol Neurosurg Psychiatry 56: 241-244. https://doi.org/10.1136/jnnp.56.3.241
2. Abbadessa G, Brigo F, Clerico M, De Mercanti S, Trojsi F, et al. (2022) Digital therapeutics in neurology. J Neurol 269:1209-1224. https://doi.org/10.1007/s00415-021-10608-4
3. Khirasaria R, Singh V, Batta A (2020) Exploring digital therapeutics: the next paradigm of modern health-care industry. Perspect Clin Res 11: 54-58.
4. Wu CW, Seo HJ, Cohen LG (2006) Influence of electric somatosensory stimulation on paretic-hand function in chronic stroke. Arch Phys Med Rehabil 87: 351-357. https://doi.org/10.1016/j.apmr.2005.11.019
5. Celnik P, Hummel F, Harris-Love M, Wolk R, Cohen LG (2007) Somatosensory stimulation enhances the effects of training functional hand tasks in patients with chronic stroke. Arch Phys Med Rehabil 88: 1369-1376. https://doi.org/10.1016/j.apmr.2007.08.001
6. Choi MJ, Kim H, Nah HW, Kang DW (2019) Digital therapeutics: emerging new therapy for neurologic deficits after stroke. J Stroke 21: 242-258. https://doi.org/10.5853/jos.2019.01963
7. Subramanian SK, Lourenço CB, Chilingaryan G, Sveistrup H, Levin MH (2013) Arm motor recovery using a virtual reality intervention in chronic stroke: randomized control trial. Neurorehabil Neural Repair 27: 13-23. https://doi.org/10.1177/1545968312449695
8. Fernández-González P, Carratalá-Tejada M, Monge-Pereira E, Collado-Vázquez S, Sánchez-Herrera Baeza P, et al. (2019) Leap motion controlled video game-based therapy for upper limb rehabilitation in patients with Parkinson's disease: a feasibility study. J Neuroeng Rehabil 16: 133. https://doi.org/10.1186/s12984-019-0593-x
9. Adamovich SV, Fluet GG, Tunik E, Merians AS (2009) Sensorimotor training in virtual reality: a review. NeuroRehabilitation 25: 29-44. https://doi.org/10.3233/NRE-2009-0497
10. Kim SI, Song IH, Cho S, Kim IY, Ku J, et al. (2013) Proprioception rehabilitation training system for stroke patients using virtual reality technology. In 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Osaka, Japan.

11. Kalron A, Fonkatz I, Frid L, Baransi H, Achiron A (2016) The effect of balance training on postural control in people with multiple sclerosis using the CAREN virtual reality system: a pilot randomized controlled trial. J Neuroeng Rehabil 13: 13. https://doi.org/10.1186/s12984-016-0124-y

12. Garcia-Agundez A, Folkerts AK, Konrad R, Caserman P, Tregel T, et al. (2019) Recent advances in rehabilitation for Parkinson's disease with exergames: a systematic review. J Neuroeng Rehabil 16: 17. https://doi.org/10.1186/s12984-019-0492-1

13. Ben-Sadoun G, Sacco G, Manera V, Bourgeois J, König A, et al. (2016) Physical and cognitive stimulation using an exergame in subjects with normal aging, mild and moderate cognitive impairment. J Alzheimers Dis 53: 1299-1314. https://doi.org/10.3233/JAD-160268

14. Cannell J, Jovic E, Rathjen A, Lane K, Tyson AM, et al. (2018) The efficacy of interactive, motion capture-based rehabilitation on functional outcomes in an inpatient stroke population: a randomized controlled trial. Clin Rehabil 32: 191-200. https://doi.org/10.1177/0269215517720790

15. Yazgan YZ, Tarakci E, Tarakci D, Ozdincler AR, Kurtuncu M (2020) Comparison of the effects of two different exergaming systems on balance, functionality, fatigue, and quality of life in people with multiple sclerosis: a randomized controlled trial. Mult Scler Relat Disord 39: 101902. https://doi.org/10.1016/j.msard.2019.101902

16. Liao YY, Yang YR, Cheng SJ, Wu YR, Fuh JL, et al. (2015) Virtual reality–based training to improve obstacle-crossing performance and dynamic balance in patients with Parkinson's disease. Neurorehabil Neural Repair 29: 658-667. https://doi.org/10.1177/1545968314562111

17. Ribas CG, da Silva LA, Corrêa MR, Teive HG, Valderramas S (2017) Effectiveness of exergaming in improving functional balance, fatigue and quality of life in Parkinson's disease: a pilot randomized controlled trial. Parkinsonism Relat Disord 38: 13-18. https://doi.org/10.1016/j.parkreldis.2017.02.006

18. Rahe J, Petrelli A, Kaesberg S, Fink GR, Kessler J, et al. (2015) Effects of cognitive training with additional physical activity compared to pure cognitive training in healthy older adults. Clin Interv Aging 10: 297-310. https://doi.org/10.2147/CIA.S74071

19. Ozdogar AT, Ertekin O, Kahraman T, Yigit P, Ozakbas S (2020) Effect of video-based exergaming on arm and cognitive function in persons with multiple sclerosis: a randomized controlled trial. Mult Scler Relat Disord 40: 101966. https://doi.org/10.1016/j.msard.2020.101966

20. McEwen D, Taillon-Hobson A, Bilodeau M, Sveistrup H, Finestone H (2014) Virtual reality exercise improves mobility after stroke: an inpatient randomized controlled trial. Stroke 45: 1853-1855. https://doi.org/10.1161/STROKEAHA.114.005362

21. Carabeo CGG, Dalida CMM, Padilla EMZ, Rodrigo MMT (2014) Stroke patient rehabilitation: a pilot study of an android-based game. Simul Gaming 45: 151-166. https://doi.org/10.1177/1046878114531102

22. Schneider S, Schönle PW, Altenmüller E, Münte TF (2007) Using musical instruments to improve motor skill recovery following a stroke. J Neurol 254: 1339-1346. https://doi.org/10.1007/s00415-006-0523-2

23. Frevel D, Mäurer M (2014) Internet-based home training is capable to improve balance in multiple sclerosis: a randomized controlled trial. Eur J Phys Rehabil Med 51: 23-30.

24. Marziniak M, Brichetto G, Feys P, Meyding-Lamadé U, Vernon K, et al. (2018) The use of digital and remote communication technologies as a tool for multiple sclerosis management: narrative review. JMIR Rehabil Assist Technol 5: e7805. https://doi.org/10.2196/rehab.7805

25. Bonavita S, Sacco R, Della Corte M, Esposito S, Sparaco M, et al. (2015) Computer-aided cognitive rehabilitation improves cognitive performances and induces brain functional connectivity changes in relapsing remitting multiple sclerosis patients: an exploratory study. J Neurol 262: 91-100. https://doi.org/10.1007/s00415-014-7528-z

26. Westerberg H, Jacobaeus H, Hirvikoski T, Clevberger P, Östensson ML, et al. (2007) Computerized working memory training after stroke – a pilot study. Brain Inj 21: 21-29. https://doi.org/10.1080/02699050601148726

27. Lundqvist A, Grundström K, Samuelsson K, Rönnberg J (2010) Computerized training of working memory in a group of patients suffering from acquired brain injury. Brain Inj 24: 1173-1183. https://doi.org/10.3109/02699052.2010.498007

28. Des Roches CA, Balachandran I, Ascenso EM, Tripodis Y, Kiran S (2015) Effectiveness of an impairment-based individualized rehabilitation program using an iPad-based software platform. Front Hum Neurosci 8: 1015. https://doi.org/10.3389/fnhum.2014.01015

29. De Luca R, Russo M, Naro A, Tomasello P, Leonardi S, et al. (2018) Effects of virtual reality-based training with BTs-Nirvana on functional recovery in stroke patients: preliminary considerations. Int J Neurosci 128: 791-796. https://doi.org/10.1080/00207454.2017.1403915

30. Palmer R, Enderby P, Cooper C, Latimer N, Julious S, et al. (2012) Computer therapy compared with usual care for people with long-standing aphasia poststroke: a pilot randomized controlled trial. Stroke 43: 1904-1911. https://doi.org/10.1161/STROKEAHA.112.650671

31. Doesborgh S, van de Sandt-Koenderman M, Dippel D, van Harskamp F, Koudstaal P, et al. (2004) Cues on request: the efficacy of Multicue, a computer program for wordfinding therapy. Aphasiology 18: 213-222. https://doi.org/10.1080/02687030344000580

32. Steele RD, Baird A, McCall D, Haynes L (2014) Combining teletherapy and online language exercises in the treatment of chronic aphasia: an outcome study. Int J Telerehabil 6: 3-20. https://doi.org/10.5195/ijt.2014.6157

33. Robert P, Manera V, Derreumaux A, Montesino MFY, Leone E, et al. (2020) Efficacy of a web app for cognitive training (MeMo) regarding cognitive and behavioral performance in people with neurocognitive disorders: randomized controlled trial. J Med Internet Res 22: e17167. https://doi.org/10.2196/17167

34. Leuner B, Gould E (2010) Structural plasticity and hippocampal function. Annu Rev Psychol 61: 111-140. https://doi.org/10.1146/annurev.psych.093008.100359

35. Knaepen K, Goekint M, Heyman EM, Meeusen R (2010) Neuroplasticity — exercise-induced response of peripheral brain-derived neurotrophic factor: a systematic review of experimental studies in human subjects. Sports Med 40: 765-801. https://doi.org/10.2165/11534530-000000000-00000

36. Voss MW, Prakash RS, Erickson KI, Basak C, Chaddock L, et al. (2010) Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. Front Aging Neurosci 2: 1803. https://doi.org/10.3389/fnagi.2010.00032

37. Voss MW, Chaddock L, Kim JS, VanPatter M, Pontifex MB, et al. (2011) Aerobic fitness is associated with greater efficiency of the network underlying cognitive control in preadolescent children. Neuroscience 199: 166-176. https://doi.org/10.1016/j.neuroscience.2011.10.009

38. Ruiz-Fernández A, Junco-Guerrero M, Cantón-Cortés D (2021) Exploring the mediating effect of psychological engagement on the relationship between child-to-parent violence and violent video games. Int J Environ Res Public Health 18: 2845. https://doi.org/10.3390/ijerph18062845

39. Drummond A, Sauer JD, Ferguson CJ (2020) Do longitudinal studies support long-term relationships between aggressive game play and youth aggressive behaviour? A meta-analytic examination. Royal Soc Open Sci 7: 200373. https://doi.org/10.1098/rsos.200373

40. Sahraie A, Smania N, Zihl J (2016) Use of NeuroEyeCoach™ to improve eye movement efficacy in patients with homonymous visual field loss. Biomed Res Int 2016: 5186461. https://doi.org/10.1155/2016/5186461

41. Sato G, Villani G, Piccolo E, Tiso F (2014) Modified visiocoach training in hemianopia. Invest Ophthalmol Vis Sci 55: 4132-4132.

42. Cavanaugh MR, Huxlin KR (2017) Visual discrimination training improves Humphrey perimetry in chronic cortically induced blindness. Neurology 88: 1856-1864. https://doi.org/10.1212/WNL.0000000000003921

43. Kim H, Cho NB, Kim J, Kim KM, Kang M, et al. (2020) Implementation of a home-based mHealth app intervention program with human mediation for swallowing tongue pressure strengthening exercises in older adults: longitudinal observational study. JMIR Mhealth Uhealth 8: e22080. https://doi.org/10.2196/22080

44. Miles A, Jardine M, Johnston F, de Lisle M, Friary P, et al. (2017) Effect of Lee Silverman Voice Treatment (LSVT LOUD®) on swallowing and cough in Parkinson's disease: a pilot study. J Neurol Sci 383: 180-187. https://doi.org/10.1016/j.jns.2017.11.015

45. Giunti G, Rivera-Romero O, Kool J, Bansi J, Sevillano JL, et al. (2020) Evaluation of more stamina, a mobile app for fatigue management in persons with multiple sclerosis: protocol for a feasibility, acceptability, and usability study. JMIR Res Protoc 9: e18196. https://doi.org/10.2196/18196

46. Meyer B, Berger T, Caspar F, Beevers C, Andersson G, et al. (2009) Effectiveness of a novel integrative online treatment for depression (Deprexis): randomized controlled trial. J Med Internet Res 11: e1151. https://doi.org/10.2196/jmir.1151

47. Cuevas PEG, Davidson PM, Mejilla JL, Rodney TW (2020) Reminiscence therapy for older adults with Alzheimer's disease: a literature review. Int J Ment Health

Nurs 29: 364-371. https://doi.org/10.1111/inm.12692

48. Filoteo JV, Cox EM, Split M, Gross M, Culjat M, et al. (2018) Evaluation of ReminX as a behavioral intervention for mild to moderate dementia. In 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Honolulu, HI, USA.
49. Austin PD, Craig A, Middleton JW, Tran Y, Costa DS, et al. (2021) The short-term effects of head-mounted virtual-reality on neuropathic pain intensity in people with spinal cord injury pain: a randomised cross-over pilot study. Spinal Cord 59: 738-746. https://doi.org/10.1038/s41393-020-00569-2
50. Ichinose A, Sano Y, Osumi M, Sumitani M, Kumagaya SI, et al. (2017) Somatosensory feedback to the cheek during virtual visual feedback therapy enhances pain alleviation for phantom arms. Neurorehabil Neural Repair 31: 717-725. https://doi.org/10.1177/1545968317718268
51. Rezaei I, Razeghi M, Ebrahimi S, Kayedi S (2019) A novel virtual reality technique (Cervigame®) compared to conventional proprioceptive training to treat neck pain: a randomized controlled trial. J Biomed Phys Eng 9: 355. https://doi.org/10.31661/jbpe.v0i0.556
52. Palmer MJ, Machiyama K, Woodd S, Gubijev A, Barnard S, et al. (2021) Mobile phone-based interventions for improving adherence to medication prescribed for the primary prevention of cardiovascular disease in adults. Cochrane Database Syst Rev 3: CD012675. https://doi.org/10.1002/14651858.CD012675.pub3
53. Kamoen O, Maqueda V, Yperzeele L, Pottel H, Cras P, et al. (2020) Stroke coach: a pilot study of a personal digital coaching program for patients after ischemic stroke. Acta Neurol Belg 120: 91-97. https://doi.org/10.1007/s13760-019-01218-z
54. Requena M, Montiel E, Baladas M, Muchada M, Boned S, et al. (2019) FARMALARM: application for mobile devices improves risk factor control after stroke. Stroke 50: 1819-1824. https://doi.org/10.1161/STROKEAHA.118.024355
55. Salimzadeh Z, Damanabi S, Kalankesh LR, Ferdousi R (2019) Mobile applications for multiple sclerosis: a focus on self-management. Acta Inform Med 27: 12. https://doi.org/10.5455/aim.2019.27.12-18
56. Greiner P, Sawka A, Imison E (2015) Patient and physician perspectives on MSdialog, an electronic PRO diary in multiple sclerosis. Patient 8: 541-550. https://doi.org/10.1007/s40271-015-0140-1
57. Limmroth V, Bartzokis I, Bonmann E, Kusel P, Schreiner T, et al. (2018) The BETACONNECT™ system: MS therapy goes digital. Neurodegener Dis Manag 8: 399-410. https://doi.org/10.2217/nmt-2018-0030
58. Casson AJ (2019) Wearable EEG and beyond. Biomed Eng Lett 9: 53-71. https://doi.org/10.1007/s13534-018-00093-6
59. Taccola S, Poliziani A, Santonocito D, Mondini A, Denk C, et al. (2021) Toward the use of temporary tattoo electrodes for impedancemetric respiration monitoring and other electrophysiological recordings on skin. Sensors 21: 1197. https://doi.org/10.3390/s21041197
60. Golan D, Sagiv S, Glass-Marmor L, Miller A (2020) Mobile phone-based e-diary for assessment and enhancement of medications adherence among patients with multiple sclerosis. Mult Scler J Exp Transl Clin 6: 1-8. https://doi.org/10.1177/2055217320939309
61. DiIorio C, Bamps Y, Walker ER, Escoffery C (2011) Results of a research study evaluating WebEase, an online epilepsy self-management program. Epilepsy Behav 22: 469-474. https://doi.org/10.1016/j.yebeh.2011.07.030
62. Si Y, Xiao X, Xia C, Guo J, Hao Q, et al. (2020) Optimising epilepsy management with a smartphone application: a randomised controlled trial. Med J Aust 212: 258-262. https://doi.org/10.5694/mja2.50520