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NOVEL FORMS OF COGNITIVE REHABILITATION

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Introduction

Neuroplasticity is often defined as the neural functional and structural changes in response to experience and environmental stimulation (Shaw, Lanius and Vandendoel, 1994). Contrary to earlier views that structural brain changes do not occur after birth, evidence from research conducted over the past few decades now suggests that neuroplastic changes are present in the adult brain. One of the first studies to show this phenomenon was a study by Maguire and colleagues (1998, 2006) showing that London taxi drivers display larger grey matter volumes in neural areas associated with spatial memory than controls. Changes in neural structures appeared to be linked to repeated practice of skills needed for their profession. The same was later found for typists and musicians (see Rapibour and Raz, 2012). Such changes were not only found after repeated practice of a skill over an extended period of time, but also when extensive training or practising a specific new skill was done over a relatively short period of time, for instance learning to juggle or studying for a medical exam (ibid.). Such breakthroughs led to a new wave of studies investigating novel forms of training and stimulation techniques to induce neural changes and thereby hoping to improve cognitive functioning. The following novel forms of cognitive rehabilitation are discussed in this chapter: computer-based cognitive retraining (CBCR); non-invasive brain stimulation (NIBS); and virtual reality training (VRT).

Computer-based cognitive retraining (CBCR)

In the last ten years computer-based cognitive retraining (CBCR) has become extremely popular, not only in a clinical context but also for people in the general population wanting to improve cognitive functioning. Brain games are found in many different forms. Consumers' expectations of cognitive benefits from brain training are sky high, but the underlying evidence shows that the effects of brain games are limited to improving performance on the specific tasks involved in game-play. From a clinical point of view, it is understandable that researchers and clinicians apply brain games to improve cognitive functions after brain damage has occurred. Specifically, based on intensive repetition, CBCR is a bottom-up approach to remediation that is aimed at improving cognitive skills needed to successfully receive sensory input, process information and react as independently as possible (Li et al., 2013). CBCR is available to the patient at home and offers stimulating and tailored programmes that can be modified to the individual's progress.

Most of the studies on brain training have been done in the areas of attention and working memory. Attention is believed to be fundamental to cognitive functioning and social behaviour, and therefore to daily life functioning. The term 'executive attention' is sometimes used to link selective attention to working memory in situations requiring attentional control and focus, and neuroimaging studies suggest these two functions draw upon similar networks in the brain (Rapibour and Raz, 2012). This may be the main reason why most CBCR studies have been done in the areas of (executive) attention and working memory.

In such research, one of the first necessary steps is to explore whether patients with acquired brain injury (ABI) are capable of using computerised cognitive training programmes. Lebowitz, Dams-O'Connor and Cantor (2012) investigated the feasibility of computerised cognitive training in a pre-post pilot study in ten individuals with mild to severe traumatic brain injury (TBI) who were six months to 22 years post injury. All participants were able to use the software programme in their own environment. Participants reported subjective improvement in cognitive functioning, and small to large effect sizes on self-report measures and neuropsychological tests were found. Effects on functional tasks or activities of daily living were not measured.

In a recent review Spreij et al. (2014) reported on the findings of seven studies that investigated the effectiveness of working memory (WM) training in individuals with brain injury. In five studies the training method was implemented with the software programme Cogmed QM (Cognitive Medical Systems) (Westerberg et al., 2007). The samples contained both stroke patients and ABI patients in the chronic phase and ranged from 18 to 47 participants. WM training (40 minutes/day, five days/week) was compared to a passive control group receiving no training (Westerberg et al., 2007), a wait-list control group (Lundqvist et al., 2010), no control group (Johansson and Tornmalm, 2012), or rehabilitation as usual (Akerlund et al., 2013; Björkdahl et al., 2013). All studies found training effects in favour of the WM group on trained WM tasks and some non-trained tasks of WM and other cognitive functions such as attention. For other outcomes, such as daily life activities, occupational performance and subjective cognitive complaints, the results were mixed and inconclusive.

Li et al. (2013) used another program called Parrot Software. They conducted a quasi-experimental one-group pre-/post-test study with 12 ABI patients. Patients were offered eight 60-minute sessions using the attention and memory program components. After treatment they found significant improvement on the attention and memory scores of the Cognistat assessment, a cognitive screening tool. Outcome in other domains, such as everyday functioning, was not measured.

De Luca et al. (2014) evaluated the effects of CBCR with regard to semantic memory, verbal fluency and short-term auditory-verbal memory in ABI patients. A sample of 35 ABI patients was randomly assigned to two groups: one group received the computerised training in addition to standard rehabilitation; the other group only received standard rehabilitation. After the training, the results showed a global improvement in both groups. However, the experimental group showed greater cognitive improvement than the control group, with significant differences on nearly all neuropsychological tests conducted.

From these seven studies it can be concluded that (working) memory training is a promising rehabilitation method in improving cognitive functioning related to the tasks which are trained. However, the generalisation of training effects to daily life functioning has yet to be consistently demonstrated. Our own group drew similar conclusions after performing a systematic review into the effectiveness of cognitive interventions in healthy older adults and people with mild cognitive impairment (MCI) (Reijnders, van Heugten and van Boxtel, 2013). The results show evidence that cognitive training can be effective in improving various aspects of cognitive functioning on standardised tests assessing memory performance, executive functioning, processing speed, attention, fluid intelligence and subjective cognitive performance. However, the issue of whether the effects of cognitive interventions generalise to improvement in everyday life activities is still unresolved and needs to be addressed more explicitly in future research. Bogdanova et al. (2015) recently published a review on CBCR of attention and executive functioning in patients with ABI in which the above seven papers on memory training were included. The authors reviewed 28 papers in total and showed that significant improvements were found in 23 of the studies. The authors are positive with regard to the effects of CBCR but also state that there are multiple methodological issues to deal with and that there is a need for standardised protocols and guidelines.

For CBCR to be applied as a method for cognitive rehabilitation in patients with ABI it is also important to know what individual factors could influence the success of the intervention in this population. While there is overall support for the effectiveness of CBCR in other populations, such as children with attention deficit hyperactivity disorder (ADHD) or learning disabilities, effect sizes for the training were found to be variable, ranging from small (or even non-existent on some outcome measures) to large effects (Coyle et al., 2014; Kueider et al., 2012; Lampit et al., 2015; Melby-Lervåg and Hulme, 2013; Peijnenborgh et al., 2015). The effectiveness of CBCR was found to be influenced by numerous factors, for example, frequency and duration of the training, targeted functions (e.g. working memory or attention), type of training (home-based or group-based), type of outcome measure and age of participants (Lampit et al., 2015; Melby-Lervåg and Hulme, 2013; Peijnenborgh et al., 2015). The factors moderating treatment outcomes of CBCR have yet to be investigated for people with ABI. In addition, we believe CBCR should not be offered in isolation, because this form of rehabilitation only targets cognitive functioning and generalisation effects are not yet shown. CBCR should therefore preferably be offered in conjunction with more functional rehabilitation programmes targeting skill development and strategy use in daily activities and other problem areas such as emotional, behavioural and social functioning.

Non-invasive brain stimulation (NIBS)

Non-invasive brain stimulation has the potential to modulate brain plasticity in humans and has been proposed to enhance functioning in patients with impairments arising from neurological diseases such as neglect and aphasia after stroke and motor and non-motor consequences in Parkinson's disease (Schulz et al., 2013). Different neurophysiologic strategies to increase the activity of the injured brain area have been proposed, mainly using Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS). TMS is based on the principle of electromagnetic induction and causes depolarisation and hyperpolarisation in the neurons. By passing a brief electric current through a coil held over the scalp, a rapidly changing magnetic field is created which penetrates the skull and secondarily induces electric currents in particular brain regions. Lower frequency of repetitive TMS is called repetitive Transcranial Magnetic Stimulation (rTMS); this is a train of TMS pulses delivered at constant intervals on the same intensity (low-frequency 1–4 Hz, high-frequency 5–10 Hz). rTMS presents the opportunity to interact even more effectively with cortical activity (Miniussi et al., 2008). tDCS consists of placing two rubber electrodes on the scalp to allow a weak direct current to flow from anode to cathode. The electrical stimulus that reaches the brain is of enough intensity to modify the level of spontaneous neuronal excitability and activity by changing the resting membrane potential. tDCS is easier to apply and less expensive than TMS (Johansson, 2011). An important drawback of NIBS, however, is the risk of evoking seizures.

Several studies have identified that altering cortical activity by cortical stimulation can positively affect cognitive performance and may therefore improve rehabilitation outcome (Miniussi et al., 2008). The therapeutic strategy of NIBS consists of modulating neural organisation, allowing for the formation of functionally appropriate neural connections and enhancing behavioural recovery (Villamar et al., 2012). Preliminary evidence suggests that NIBS may play a role in treating unilateral neglect (Lim et al., 2010; Nyffeler et al., 2009) and aphasia (Naeser, et al., 2005; Szaflarski et al., 2011) after stroke.

With respect to memory improvement in healthy participants, a recent review concluded that rTMS and tDCS applied on the dorsolateral prefrontal cortex significantly improve performance on measures of WM performance, including reaction time and/or accuracy (Brunoni and Vanderhasselt, 2014). They included 12 studies involving 33 experiments in total. NIBS was significantly associated with faster response times (RTs), higher percentage of correct responses and lower percentage of error responses. tDCS (versus rTMS) presented only an improvement in RT, and not in accuracy. This review shows a recent interest in the use of NIBS to improve memory function and shows evidence that brain stimulation delivered to the prefrontal cortices increases neural efficiency related to WM in healthy participants.

Recently, clinical studies have shown similar results with respect to memory impairments. Two small sample controlled studies examined stimulation applied over the left dorsolateral prefrontal cortex to improve cognition. In the first study, rTMS was used to study cognition and mood in 18 post-stroke patients (Kim et al., 2010). Patients were randomised into three groups (low-frequency [1 Hz] stimulation, high-frequency [10 Hz] stimulation, and sham stimulation [control]). The evaluations were conducted in all patients before and after treatment. Treatment had no significant effect on any cognitive function parameter in any of the treatment groups. However, high-frequency rTMS resulted in significantly lower Beck Depression Inventory scores relative to baseline and compared with the other two groups. rTMS is thought to induce more distant alterations in the limbic system and orbitofrontal systems or dopaminergic systems. In another study, anodal tDCS was applied over the left dorsolateral prefrontal cortex to affect the WM performance of ten post-stroke patients (Jo et al., 2009). A significant improvement in accuracy and recognition accuracy on a two-back WM task was only found in the anodal tDCS and not in the sham tDCS. These two small-sized studies show preliminary results for the potential beneficial effects of NIBS after stroke, but there is yet no evidence for functional improvement in targeted cognitive domains.

In two randomised controlled studies anodal tDCS was applied to improve cognitive functioning in TBI patients. Ulam and colleagues (2015) investigated the cumulative effects of anodal tDCS on EEG oscillations, attention and WM function. The EEG revealed immediate and cumulative changes in brain oscillations for the active tDCS as compared to the sham group. EEG changes in the active tDCS group were correlated with improved performance on neuropsychological tests. In a second study cumulative anodal tDCS was applied over the left dorsolateral prefrontal cortex to enhance memory and attention in 23 patients with TBI in a randomised design where both groups received 15 days of cognitive training and the experimental group also received tDCS (Leśniak et al., 2014). A battery of memory and attention tests was administered, which included tests involving both visual and auditory modalities. Although improvements in the experimental group were larger on these tests, there were no significant differences between the groups. We can conclude therefore that results of tDCS in TBI patients are inconclusive and, again, there is no evidence for functional gains.

In one randomised pilot study the synergistic effects of both CBCR and tDCS on cognitive function (attention and memory) in post-stroke patients were investigated (Park et al., 2013). Both groups received CBCR for 30 minutes a day (15 minutes of memory training, 15 minutes of attention training) five times a week until discharge. The experimental group also received tDCS. All patients were evaluated using the Korean Mini-Mental State Examination and the Seoul Computerized Neuropsychological Test (SCNT). The SCNT was composed of ten measurements assessing verbal memory, visuospatial memory, attention and visuo-motor coordination. The patients in the tDCS group showed a significant improvement in only two attention tests of the SCNT, but not on memory tests.

To sum up, only one study (Jo et al., 2009) found evidence of significant gains in verbal WM performance after the use of NIBS in stroke patients. Four studies (Kim et al., 2010; Leśniak et al., 2014; Park et al., 2013; Ulam et al., 2015) did not find sufficient evidence to support the efficacy of NIBS for enhancing rehabilitation of memory in ABI patients.

In patients with neglect NIBS is now offered to both the ipsilateral and the contralateral hemisphere, because evidence shows that there occurs depression of activity in the parietal areas of the right (lesioned) hemisphere and overactivation of these homologous areas in the left hemisphere, leading to interhemispheric rivalry (Fasotti and Van Kessel, 2013). Previously, NIBS studies aimed for inhibition of the left hemisphere. rTMS aiming for inhibition of the left hemisphere was offered in different small size studies showing short-term effects on paper and pencil tasks such as line bisection (Brighina et al., 2003; Koch et al., 2008; Lim et al., 2010; Oliveri et al., 2001; Shindo et al., 2006; Song et al., 2009). Ko et al. (2008) investigated the effect of tDCS applied to the right hemisphere and showed similar results. Although promising, most of the effects are transient and thus lasting therapeutic benefits are yet to be shown.

Recently, Elsner et al. (2015) performed a Cochrane review on the effectiveness of tDCS for improving aphasia in patients with stroke. In total, 12 RCTs involving 136 stroke patients with aphasia were included in the review. None of the studies measured functional communication (i.e. skill performance in a real life communication setting). The results did not indicate that tDCS was favourable in terms of improving language impairment or cognitive functioning. The authors concluded that currently there is no evidence to suggest that tDCS can enhance the treatment effects of speech and language therapy for aphasia.

Virtual reality training (VRT)

Virtual reality (VR) has been defined as 'an advanced form of human-computer interface that allows the user to "interact with" and become "immersed in" a computer-generated environment in a naturalistic fashion' (Weis, 2006, pp. 182–197). Virtual environments represent many real-life situations and are programmed to record accurate measurements of the individual's performance assessing the underlying function (Brooks and Rose, 2003). VR is an interactive computer technology that can create the illusion of being in an artificial world. An fMRI study indicated that virtual-based environments are able to activate the same related brain parts as those activated in the real environment (You et al., 2005). Some evidence of transfer of learnt skills from VR training to real-life situations has been reported, which supports the ecological validity of this training format (Brooks and Rose, 2003). VR can be used to obtain a realistic and controlled assessment of memory and executive impairment in a rehabilitation setting (Brooks et al., 2004). VR in rehabilitation is not only useful as an assessment tool, but also has the potential to offer an effective training method.

In stroke rehabilitation VR has mainly been used to train motor functioning. In a Cochrane review Laver et al. (2011) found limited evidence that VR and interactive video gaming can be applied to improve arm function and ADL function. In a recent update of their review (Laver et al., 2015), more studies were included, but the same conclusions were drawn.

Fasotti and van Kessel (2013) summarised studies on VR training in their review on novel insights in neglect rehabilitation. They found that VR has been used to simulate grasping in space, sometimes using a hand-motion tracking device (Ansuini et al., 2006; Castiello et al., 2004; Sedda et al., 2012). Smith et al. (2007) offered four patients with mild neglect a computer game in which their own arm movements were transformed into the movements of an avatar on the screen. After six weeks of training, small improvements in paper and pencil tasks were found. In an RCT with 24 neglect patients, Kim et al. (2011) investigated conventional neglect training versus interactive computer gaming (30 minutes a day, five days a week for three weeks). A small but favourable effect of the VR training was found. Webster et al. (2001), Katz et al. (2005) and Kim et al. (2007) used desktop computer programs to simulate wheelchair obstacle courses and street crossing. Real life performance in both tasks improved after training. However, a large scale RCT (n=69) (Akinwuntan et al., 2010) found no differences between simulator-based driving-related training and non-computer-based cognitive training for 15 hours over five weeks. Similar results were found by van Kessel et al. (2013), who compared visual scanning training to a condition consisting of a combination of visual scanning training and a VR driving simulator task in 29 patients with subacute right hemisphere stroke.

In the field of memory rehabilitation, two relevant case studies were performed. Caglio et al. (2012) described a qualitative case study of a 24-year-old man with TBI presenting memory deficits and evaluated the efficacy of a 3D interactive VR navigational training programme measuring neuropsychological changes and changes in neural activation using fMRI. Visual-spatial memory improvement appeared to be present both immediately after the VR navigational training and at follow-up testing. The functional neuroimaging assessment showed increased activity in the left hippocampus and the right parahippocampal cortex compared to the pre-training assessment. Yip and Man (2009) examined the usability and efficacy of a VR-based skills training programme for people with ABI in four cases. A VR-based community living skills training programme of ten sessions was conducted, consisting of key cognitive training elements (including memory) to promote generalisation to real-life situations. Outcome measures consisted of built-in parameters to document the participants' performance during each session and the Neurobehavioural Cognitive Status Examination. An improvement on these outcome measures was found (not statistically tested) and supported by the subjective experiences of the participants. All four patients showed improvement in skills acquisition on the community living tasks and in memory performance on neuropsychological tests.

Four years later the same authors evaluated the effectiveness of a VR-based memory training in a larger sample (n=37) (Yip and Man, 2013). The experimental group received a 12-session VR-based programme with prospective memory tasks and the control group was not provided with a VR-based training, but had regular reading and table game activities during the treatment phase. Neuropsychological tests were administered to measure the effects of the treatment on prospective memory skill acquisition (VR-based assessment by outcome parameters) and executive function. The results showed significantly larger changes in both VR-based and real-life prospective memory outcome measures after the VR-based training. Related cognitive attributes, such as executive functions and semantic fluency, showed a significantly greater improvement after VR-based training compared with the control group.

Larson et al. (2014) conducted a systematic review on VR interventions in cognitive rehabilitation. They reviewed 17 studies over the past five years with only a few RCTs. Some of the studies described above were included in this review. They conclude that some applications are effective in treating cognitive deficits following neurological conditions, but further study is necessary. They promote studies into the application of enriched virtual environments, including haptic sensory input and gaming systems for telerehabilitation.

Thus, there are some promising preliminary findings regarding the efficacy of VR-based training for improvement in memory function. However, it is difficult to draw any firm conclusions due to the small number of studies and methodological limitations associated with these studies. Moreover, future studies should include more functional outcome measures.

Conclusions

The evidence on novel forms of cognitive rehabilitation is growing. Overall there was consistent evidence that CBCR can be effective in improving memory function on trained tasks, and tasks related to the trained tasks, in individuals with ABI, but only a few studies found a generalised effect to non-trained tasks. Given the number of studies and the number of controlled studies, this novel form of rehabilitation seems most promising. The studies assessing NIBS did not find evidence supporting the use of NIBS for improving memory or language function. The few small size studies using VR-based training seem to show preliminary effects in retraining the underlying function in a virtual real-life environment and facilitating the generalisation to functional levels. However, these results should be considered as preliminary because of the limited number of studies available, the low methodological quality and the low number of ABI patients. Moreover, daily life functioning and long-term effects have not been investigated thoroughly or consistently. For all reported treatment techniques, further high quality studies into effectiveness are needed. In the present overview, CBCR, NIBS and VR were studied separately. It is also interesting to investigate whether combinations of treatments would lead to better outcomes. For ABI patients, these studies have not been performed yet, but Park et al. (2014) showed that a combination of CBCR and anodal tDCS led to higher accuracy of the verbal working memory task and better performance of the digit span forward test than CBCR combined with sham tDCS in healthy older adults. It is important to note, however, that these forms of rehabilitation are primarily focused on alleviating cognitive impairment. Neuropsychological rehabilitation is aimed at a broader spectrum of human functioning, also taking into account emotional, behavioural and social functioning, with the ultimate goal to optimise the participation and quality of life of both patients and caregivers. Although promising, these methods of rehabilitation should therefore always be offered only in combination with comprehensive neuropsychological rehabilitation programmes.

References

Akinwuntan, A.E., Devos, H., Verheyden, G., Baten, G., Kiekens, C., Feys, H. et al. (2010). Retraining moderately impaired stroke survivors in driving-related visual attention skills. *Top Stroke Rehabilitation, 17*, 328–336.

Ansuini, C., Pierno, A.C., Lusher, D. and Castiello, U. (2006).Virtual reality applications for the remapping of space in neglect patients. *Restorative Neurology and Neuroscience, 24*, 431–441.

Ȧkerlund, E., Esbjörnsson, E., Sunnerhagen, K.S. and Björkdahl, A. (2013). Can computerized working memory training improve impaired working memory, cognition, and psychological health? *Brain Injury, 27(13–14)*, 1649–1657.

Björkdahl, A., Åkerlund, E., Svensson, S. and Esbjörnsson, E. (2013). A randomized study computerized working memory training and effects on functioning in everyday life for patients with brain injury. *Brain Injury, 27(13–14)*, 1658–1665.

Brighina, F., Bisiach, E., Oliveri, M., Piazza, A., LaBua, V., Daniele, O. et al. (2003). 1 Hz repetitive transcranial magnetic stimulation of the unaffected hemisphere ameliorates contralesional visuospatial neglect in humans. *Neuroscience Letters, 336*, 131–133.

Bogdanova, Y., Yee, M.K., Ho, V.T. and Cicerone, K.D. (2015). Computerized cognitive rehabilitation of attention and executive function in acquired brain injury: a systematic review. *Journal of Head Trauma Rehabilitation*, Dec 2 (epub ahead of print).

Brooks, B.M. and Rose, F.D. (2003). The use of virtual reality in memory rehabilitation: current findings and future directions. *Neurorehabilitation, 18*, 147–157.

Brooks, B.M., Rose, F.D., Potter, J., Attree, E.A., Jayawardena, S. and Morling, A. (2004). Assessing stroke patients' ability to remember to perform actions in the future using virtual reality. *Brain Injury, 18*, 391–401.

Brunoni, A.R. and Vanderhasselt, M.-A. (2014). Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. *Brain and Cognition, 86*, 1–9.

Caglio, M., Latini-Corazzini, L., D'Agata, F., Cauda, F., Sacco, K., Monteverdi, S. et al. (2012). Virtual navigation for memory rehabilitation in a traumatic brain injured patient. *Neurocase: The Neural Basis of Cognition, 18(2)*, 123–131.

Castiello, U., Lusher, D., Burton, C., Glover, S. and Disler, P. (2004). Improving left hemispatial neglect using virtual reality. *Neurology, 62*, 1958–1962.

Coyle, H., Traynor, V. and Solowij, N. (2014). Computerized and virtual reality cognitive training for individuals at high risk of cognitive decline: systematic review of the literature. *American Journal of Geriatric Psychiatry, 23(4)*, 335–359.

De Luca, R., Calabrò, R.S., Gervasi, G., De Salvo, S., Bonanno, L., Corallo, F., De Cola. M.C. and Bramnti, P. (2014). Is computer-assisted training effective in improving rehabilitative outcomes after brain injury? A case-control hospital-based study. *Disability and Health Journal, 7*, 356–360.

Elsner, B., Kugler, J., Pohl, M. and Mehrholz, J. (2015). Transcranial direct current stimulation (tDCS) for improving aphasia in patients with aphasia after stroke. *Cochrane Database Systematic Reviews, 5*, CD009760.

Fasotti, L. and van Kessel, M. (2013). Novel insights in the rehabilitation of neglect. *Frontiers in Human Neuroscience, 7*, 1–8.

Jo, J.M., Kim, M.H., Ohn, S.H., Joen, B. and Lee, K.H. (2009). Enhancing the working memory of stroke patients using tDCS. *American Journal of Physical Medicine and Rehabilitation, 88*, 404–409.

Johansson, B.B. (2011). Current trends in stroke rehabilitation: a review with focus on Brain Plasticity. *Acta Neurologica Scandinavica, 123*, 147–159.

Johansson, B.B. and Tornmalm M. (2012). Working memory training for patients with acquired brain injury: effects in daily life. *Scandinavian Journal of Occupational Therapy, 19(2)*, 176–183.

Katz, N., Ring, H., Naveh, Y., Kizony, R., Feintuch, U. and Weiss, P.L. (2005). Inter-active virtual environment training for safe street crossing of right hemisphere stroke patients with unilateral spatial neglect. *Disability and Rehabilitation, 27*, 1235–1243.

Kim, J., Kim, K., Kim, D.Y., Chang, W.H., Park, C.I., Ohn, S.H. et al. (2007).Virtual environment training system for rehabilitation of stroke patients with unilateral neglect: crossing the virtual street. *Cyberpsychology and Behavior, 10*, 7–15.

Kim, B.R., Kim, D.Y., Chun, M.H., Yi, J.H. and Kwon, J.S. (2010). Effect of repetitive transcranial magnetic stimulation on cognition and mood in stroke patients: a double-blind, sham-controlled trial. *American Journal of Physical Medicine and Rehabilitation, 89*, 362–368.

Kim, Y.M., Chun, M.H., Yun, G.J., Song, Y.J. and Young, H.E. (2011).The effect of virtual reality training on unilateral spatial neglect in stroke patients. *American Rehabilitation Medicine, 35*, 309–315.

Ko, M.H., Han, S.H., Park, S.H., Seo, J.H. and Kim, Y.H. (2008). Improvement of visual scanning after DC brain polarization of parietal cortex in stroke patients with spatial neglect. *Neuroscience Letters, 448*, 171–174.

Koch, G., Oliveri, M., Cheeran, B., Ruge, D., LoGerfo, E., Salerno, S. et al. (2008). Hyperexcitability of parietal-motor functional connections in the intact left-hemisphere of patients with neglect. *Brain, 131*, 3147–3155.

Kueider, A.M., Parisi, J.M., Gross, A.L. and Rebok, G.W. (2012). Computerized cognitive training with older adults: a systematic review. *PLoS One, 7(7)*, e40588.

Lampit, A., Valenzuela, M. and Gates, N.J. (2015). Computerized cognitive training is beneficial for older adults. *Journal of the American Geriatric Society, 63(12)*, 2610–2612.

Larson, E.B., Feigon, M., Gagliardo, P. and Dvorkin, A.Y. (2014).Virtual reality and cognitive rehabilitation: a review of current outcome research. *NeuroRehabilitation, 34(4)*, 759–72.

Laver, K.E., George, S., Thomas, S., Deutsch, J.E. and Crotty, M. (2011). Virtual reality for stroke rehabilitation. *Cochrane Database Systematic Reviews*, 9.

Laver, K.E., George, S., Thomas, S., Deutsch, J.E. and Crotty, M. (2015). Virtual reality for stroke rehabilitation. *Cochrane Database Systematic Reviews*, 2.

Lebowitz, M.S., Dams-O'Connor, K. and Cantor, J.B. (2012). Feasibility of computerized brain plasticity-based cognitive training after traumatic brain injury. *Journal of Rehabilitation Research and Development, 49(10)*, 1547–1556.

Leśniak, M., Polanowska, K., Seniów, J. and Członkowska, A. (2014). Effects of repeated anodal tDCS coupled with cognitive training for patients with severe traumatic brain injury: a pilot randomized controlled trial. *Journal of Head Trauma Rehabilitation, 29(3)*, 20–29.

Li, K., Robertson, J., Ramos, J. and Gella, S. (2013). Computer-based cognitive retraining for adults with chronic acquired brain injury: a pilot study. *Occupational Therapy in Health Care, 27(4)*, 333–344.

Lim, J.Y., Kang, E.K. and Paik, N.J. (2010). Repetitive transcranial magnetic stimulation to hemispatial neglect in patients after stroke: an open-label pilot study. *Journal of Rehabilitation Medicine, 42*, 447–452.

Lundqvist, A., Grundström, K., Samuelsson, K. and Rönnberg, J. (2010). Computerized training of working memory in a group of patients suffering from acquired brain injury. *Brain Injury, 24(10)*, 1173–1183.

Maguire, E.A., Burgess, N., Donnett, J.G., Frackowiak, R.S.J., Frith, C.D. and O'Keefe, J. (1998). Knowing where and getting there: a human navigation network. *Science, 280(5365)*, 921–924.

Maguire, E.A., Woollett, K. and Spiers, H.J. (2006). London taxi drivers and bus drivers: a structural MRI and neuropsychological analysis. *Hippocampus, 16(12)*, 1091–1101.

Melby-Lervåg, M. and Hulme, C. (2013). Is working memory training effective? A meta-analytic review. *Developmental Psychology, 49(2)*, 270–291.

Miniussi, C., Cappa, S. F., Coohen, L., Floel, A., Fregni, F., Nitsch, M.A. et al. (2008). Efficacy of repetitive transcranial magnetic stimulation/transcranial direct current stimulation in cognitive neurorehabilitation. *Brain Stimulation, 1*, 326–336.

Naeser, M.A., Martin, P.I., Nicholas, M. et al. (2005). Improved picture naming in chronic aphasia after TMS to part of right Broca's area: an open-protocol study. *Brain and Language, 93*, 95–105.

Nyffeler, T., Cazzoli, D., Hess, C.W. and Muri, R.M. (2009). One session of repeated parietal theta burst stimulation trains induces long-lasting improvement of visual neglect. *Stroke, 40*, 2791–2796.

Oliveri, M., Bisiach, E., Brighina, F., Piazza, A., LaBua, V., Buffa, D. et al. (2001). rTMS of the unaffected hemisphere transiently reduces contralesional visuospatial hemineglect. *Neurology, 57*, 1338–1340.

Park., S.-H., Koh, E.-J., Choi, H-Y. and Ko, M-H. (2013). A double-blind, sham-controlled, pilot study to assess the effects of the concomitant use of transcranial direct current stimulation with the computer assisted cognitive rehabilitation to the prefrontal cortex on cognitive functions in patients with stroke. *Journal of the Korean Neurosurgical Society, 54*, 484–488.

Park, S.H., Seo, J.H. Kim, Y. and Ko, M.H. (2014). Long-term effects of transcranial direct current stimulation combined with computer-assisted cognitive training in healthy older adults. *Neuroreport, 25*, 122–126.

Peijnenborgh, J.C., Hurks, P.M., Aldenkamp, A.P., Vles, J.S. and Hendriksen, J.G. (2015). Efficacy of working memory training in children and adolescents with learning disabilities: a review study and meta-analysis. *Neuropsychological Rehabilitation*, 1–28 (epub ahead of print).

Rapibour, S. and Raz, A. (2012). Training the brain: fact and fad in cognitive and behavioral remediation. *Brain and Cognition, 79*, 159–179.

Reijnders, J., van Heugten, C.M. and van Boxtel, M. (2013). Cognitive interventions in healthy older adults and people with mild cognitive impairment; a systematic review. *Ageing Research Review, 12(1)*, 263–275.

Schulz, R., Gerloff, C. and Hummel, F.C. (2013). Non-invasive brain stimulation in neurological diseases. *Neuropharmacology, 64*, 579–587.

Sedda, A., Borghese, N.A., Ronchetti, M., Mainetti, R., Pasotti, F., Beretta, G. et al. (2012). Using virtual reality to rehabilitate neglect. *Behavior Neurology, 26*, 183–185.

Shaw, C.A., Lanius, R.A. and Vandendoel, K. (1994). The origin of synaptic neuroplasticity – crucial molecules or a dynamical cascade. *Brain Research Reviews, 19(3)*, 241–263.

Shindo, K., Sugiyama, K., Huabao, L., Nishijima, K., Kondo, T. and Izumi, S. (2006). Long-term effect of low-frequency repetitive transcranial magnetic stimulation over the unaffected posterior parietal cortex in patients with unilateral spatial neglect. *Journal of Rehabilitation Medicine, 38*, 65–67.

Smith, J., Hebert, D. and Reid, D. (2007). Exploring the effects of virtual reality on unilateral neglect caused by stroke: four case studies. *Technology and Disability, 19*, 29–40.

Song, W., Du, B., Xu, Q., Hu, J., Wang, M. and Luo, Y. (2009). Low-frequency transcranial magnetic stimulation for visual spatial neglect: a pilot study. *Journal of Rehabilitation Medicine, 41*, 162–165.

Spreij, L., Visser-Meily, J., van Heugten, C.M. and Nijboer, T. (2014). Novel insights into the rehabilitation of memory post acquired brain injury: a systematic review. *Frontiers in Human Neuroscience, 8(93)*, 1–19.

Szaflarski, J.P., Vannest, J., Wu, S.W., DiFrancesco, M.W., Banks, C. and Gilbert, D.L. (2011). Excitatory repetitive transcranial magnetic stimulation induces improvements in chronic post-stroke aphasia. *Medical Science Monitor, 17*, 132–139.

Ulam, F., Shelton, C., Richards, L., Davis, L., Hunter, B., Fregni, F. and Higgens, K. (2015). Cumulative effects of transcranial direct current stimulation on EEG oscillations and attention/working memory during subacute neurorehabilitation of traumatic brain injury. *Clinical Neurophysiology, 126(3)*, 486–496.

Van Kessel, M.E., Geurts, A.C.H., Brouwer, W.H. and Fasotti, L. (2013). Visual scanning training for neglect after stroke with and without a computerized lane tracking dual task. *Frontiers of Human Neuroscience, 7*, 358.

Villamar , M.F., Portilla, A.S.P., Fregni, F. and Zafonte, R., (2012). Nonivasive brain stimulation to modulate neuroplasticity in traumatic brain injury. *Neuromodulation: Technology at Neural Interface, 15*, 326–338.

Webster, J.S., McFarland, P.T., Rapport, L.J., Morrill, B., Roades, L.A. and Abadee, P.S. (2001). Computer-assisted training for improving wheelchair mobility in unilateral neglect patients. *Archives of Physical Medicine and Rehabilitation, 82*, 769–775.

Weis, P., Kizoury, R., Feintuch, U. and Katz, N. (2006). Virtual reality in neurorehabilitation. In M. Selzer, L. Cohen, F. Gage, S. Clarke and P. Duncan (Eds.), *Textbook of Neural Repair and Rehabilitation*, pp. 182–197. Cambridge: Cambridge University Press.

Westerberg, H., Jacobaeus, H. Hirvikoski, T., Clevberger, P., Ostensson, M,-L., Bartfai, A. et al. (2007). Computerized working memory training after stroke – a pilot study. *Brain Injury, 21*, 21–29.

Yip, B.C.B. and Man, D.W.K. (2009). Virtual reality-based prospective memory training program for people with acquired brain injury. *NeuroRehabilitation, 32*, 103–115.

Yip, B.C.B. and Man, D.W.K. (2013). Virtual reality (VR)-based community living skills training for people with acquired brain injury: a pilot study. *Brain Injury, 23*, 1017–1026.

You, S.H., Jang, S.H., Kim, Y.H., Hallett, M., Ahn, S.H., Kwon, Y.H. et al. (2005). Virtual Reality-induced cortical reorganization and associated locomotor recovery in chronic stroke: an experimenter-blind randomized study. *Stroke, 36*, 1166–1171.