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Cognitive Rehabilitation in Stroke Patients: a Systematic Review

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ABBREVIATIONS

AT: Alberts Test
BIT-C: Behavioral Inattention Test Conventional
CBS: Catherine Bergego Scale
cTBS: Continuous Theta Burst Stimulation
CT: Computed Tomography
DALY: Disability-Adjusted Life-Year
EEG: Electroencephalography
FIM: Functional Independence Measure
fMRI: Functional Magnetic Resonance Imaging
GBD: Global Burden of Disease
iTBS: Intermittent Theta Burst Stimulation
IVR: Immersive Virtual Reality
LBT: Line Bisection Test
LH PPC: Left Hemisphere Posterior Parietal Cortex
MAC: Motor Activity Chart
MMSE: Mini-Mental State Examination
MRI: Magnetic Resonance Imaging
MVPT-3: Motor-Free Visual Perception Test, Third Edition
NIBS: Non-Invasive Brain Stimulation
NIVR: Non-Immersive Virtual Reality
PA: Prism Adaptation
PPC: Posterior Parietal Cortex
RCT: Randomized Controlled Trial
rTMS: Repetitive Transcranial Magnetic Stimulation
SA: Sham Adaptation
SCT: Star Cancellation Test
SIVR: Semi-Immersive Virtual Reality
TBS: Theta Burst Stimulation
tDCS: Transcranial Direct Current Stimulation
TMS: Transcranial Magnetic Stimulation
USN: Unilateral Spatial Neglect
VAN: Ventral Attention Network
VR: Virtual Reality

KEYWORDS
Visuospatial Neglect, Unilateral Spatial Neglect, Stroke, Rehabilitation

SUMMARY

Stroke is the second leading cause of death and third leading cause of disability worldwide. Cognitive impairment post stroke commonly occurs in patients with the manifestation ranging from impairment in memory, to attention, to executive function to processing speed. Thess effects can impair a patients live for years. Visuospatial neglect (USN) occurrs in around 20–82% of stroke patients. USN impairs functional recovery process and has a severely negative impact on Activities of daily living (ADL). Despite many years of research and its severe negative effects, no single intervention has proven to be the gold standard, highlighting the need for a comprehensive comparative overview.

The aim of this narrative literature review was to provide this comprehensive overview and compare the effectiveness of the most commonly researched visuospatial neglect rehabilitation techniques.

To do so the objectives were 1st to evaluate the effectiveness of prism adaptation (PA), virtual reality (VR) assisted rehabilitation, mirror therapy, robot assisted therapy, transcranial magnetic stimulation (TMS), and transcranial direct current stimulation (tDCS). 2nd compare effectiveness across modalities and 3rd identify key methodological limitations and formulate recommendations for future research.

A structured literature search was conducted in PubMed using MeSH term consisting of visuospatial neglect, stroke and most common rehabilitation interventions. Studies published between January 2015 and December 2025 which included adult stroke patient with USN were included. Included designs comprised randomized controlled trials, observational studies, systematic reviews, meta-analyses, and case reports with five or more participants. A narrative synthesis approach was adopted to accommodate the heterogeneity of interventions, outcome measures, and study designs. 18 sources were included.

Overall TMS demonstrated the most consistent and robust evidence of improvement across line bisection test, star cancellation test, and ADL. tDCS showed moderate evidence of benefits. VR assisted rehabilitation proved to be at least equivalent effectiveness when comparing with conventional therapy. Robot assisted therapy showed task specific improvements in line bisection, but they did not consistently generalize to broader functional outcomes. PA yielded mixed short-term effectiveness with no confirmed long-term benefit. Mirror therapy showed no significant effect on USN.

However, all modalities show severe limitations due to limitation in small sample sizes, heterogeneous protocols, and insufficient long term follow ups. Therefore, future research should prioritize large multicenter randomized trials, standardized outcome measures including functional scales and integrate neuroimaging.

SANTRAUKA

Insultas yra antra pagal dažnumą mirties priežastis ir trečia pagal dažnumą negalios priežastis visame pasaulyje. Po insulto dažnai pasireiškia kognityviniai sutrikimai, kurie gali apimti atminties, dėmesio, vykdomųjų funkcijų ir informacijos apdorojimo greičio sutrikimus. Šie poveikiai gali neigiamai veikti paciento gyvenimą daugelį metų. Erdvinė hemineglekto sindromas (USN)

pasireiškia maždaug 20–82% insulto pacientų. USN trukdo funkciniam atsigavimo procesui ir daro itin neigiamą poveikį kasdienės veiklos funkcijoms (ADL). Nepaisant daugelio metų tyrimų ir itin neigiamų šio sutrikimo pasekmių, nė viena intervencija neįrodė esanti aukso standartas, todėl būtina atlikti išsamią lyginamąją apžvalgą.

Šios išplėstinės literatūros apžvalgos tikslas pateikti išsamią apžvalgą ir palyginti dažniausiai tiriamų reabilitacijos metodų regimajam erdviniui neigimui koreguoti veiksmingumą.

Kelti uždaviniai buvo šie - įvertinti prizminės adaptacijos (PA), virtualiosios realybės (VR) pagrindu vykdomos reabilitacijos, veidrodžių terapijos, robotų pagalba atliekamos terapijos, transkranijinės magnetinės stimuliacijos (TMS) ir transkranijinės nuolatinės srovės stimuliacijos (angl. tNSS) veiksmingumą bei palyginti skirtingų metodų veiksmingumą, o taip pat nustatyti pagrindinius metodologinius ribotumus bei suformuluoti rekomendacijas būsimiems tyrimams.

Struktūrizuota literatūros paieška buvo atlikta PubMed duomenų bazėje naudojant MeSH terminus, regimasis erdvinis neigimas, insultas ir dažniausiai taikomi reabilitacijos metodai. Į apžvalgą buvo įtraukti 2015 m. sausio mėn. - 2025 m. gruodžio mėn. laikotarpiu paskelbti tyrimai, apimantys suaugusiuosius pacientus patyrusius insultą, kuriems pasireiškė regimasis erdvinis neigimas. Įtraukti tyrimo dizainai apėmė atsitiktinių imčių kontroliuojamus tyrimus, stebėjimo tyrimus, sistemines apžvalgas, metaanalizes ir atvejų analizes su penkiais ar daugiau dalyvių. Dėl intervencijų, rezultatų matų ir tyrimo dizainų nevienalytiškumo buvo pasirinktas išplėstinės literatūros apžvalgos metodas. Iš viso į apžvalgą įtraukta 18 šaltinių.

Apibendrinant, TMS parodė nuosekliausius ir patikimiausius pagerėjimo įrodymus pagal linijos dalijimo testą, žvaigždučių išbraukymo testą ir kasdienių veiklū atlikimo testą. tNSS parodė vidutinį naudos lygį. VR pagrindu vykdoma reabilitacija pasirodė lygiavertė įprastinei terapijai. Robotų pagalba atliekama terapija parodė specifinių užduočių atlikimo pagerėjimą atliekant linijos dalijimo testą, tačiau šie rezultatai nuosekliai neapibendrinti detalesniems funkciniams rezultatams gauti. PA naudojimas pateikė nevienodą trumpalaikį veiksmingumą ir nepatvirtintą ilgalaikę naudą. Veidrodžių terapija neturėjo reikšmingo poveikio regimajam erdviniam neigimui. Visi nagrinėti metodai turi rimtų apribojimų dėl mažų imčių dydžių, nevienalyčių protokolų ir nepakankamos ilgalaikės stebėsenos. Todėl būsimi tyrimai turėtų teikti pirmenybę dideliems daugiacentriams atsitiktinių imčių tyrimams, standartizuotiems rezultatų matams, įskaitant funkcines skales, bei integruoti neurovaizdinimo metodus.

1 INTRODUCTION

Stroke is one of the most common causes of death and disability in the 21st century with the global burden of disease 2021 estimating that amongst non-communicable diseases is the second leading cause of death and when assessed by disability-adjusted life-years lost (DALY) the third leading cause of death and disability. Additionally the absolute number of strokes increased by 70% from the years 1990-2019 (1). The estimated global cost per year is 890 billion USD and is projected to almost double by 2050 (2). Cognitive impairment post stroke commonly occurs in patients with the manifestation ranging from impairment in memory, to attention, to executive function to processing speed. Thess effects can impair a patients live for years. One of the more commonly occurring and consequences of stroke is visuospatial neglect. The estimated prevalence of visuospatial neglect varies somewhere between 20-82% depending on location, phase and time poststroke, patient sample and test used to assess (3,4). Visuospatial neglect is characterized by patients inability to perceive events on neglected side often leading to patient having difficulty initiating or performing movements towards the contralesional side, even when there is no evidence of motor system damage (5). The neural substrate of visuospatial neglect has been linked to the disruption of the right hemispheres spatial attention networks. Corbetta and Shulman argue that rather than linking unilateral spatial neglect to structural damage of specific brain regions, one should look at the physiological dysfunction of cortical networks. They particularly focus on the interaction of ventral and dorsal attention networks and suggest that both the severity and interhemispheric functional connectivity of dorsal regions are related to degree of functional connectivity or integrity of ventral/pivot regions and the degree of integrity of white matter tracts, which are likely to connect ventral and dorsal regions (6). Damage to the VAN, centered on the right temporoparietal junction and inferior frontal gyrus, can be considered the primary mechanism underlying the attentional bias characteristic of neglect. Karnath and Rorden demonstrated that the characteristic neglect symptoms are linked to damage in the right hemispheric persylvian regions and temporoparietal junction (7), implications of these findings for rehabilitation will be discussed in Section 4.

While in a portion of patients spontaneously recover their visual spatial neglect during the acute and subacute phase post stroke, this usually happens within the first weeks to months after onset, Nijboer et al. demonstrated in their systematic review that in a significant number of patients neglect symptoms remained beyond the acute phase (8) highlighting the necessity for rehabilitation. Currently a broad range of rehabilitation strategies targeting visuospatial neglect have been developed and investigated. The approaches range from perceptual and attentional training, sensory stimulation techniques, motor and limb activation to direct neurostimulation. This review primarily focuses on Prism adaptation, virtual reality assisted rehabilitation, robot assisted therapy, transcranial magnetic stimulation, transcranial direct current stimulation, optokinetic stimulation in the form of mirror therapy. With the primary aim being to give a comprehensive overview of the mentioned techniques effectiveness in the field of unilateral visuospatial neglect rehabilitation.

2 METHODS

A structured literature search was conducted to identify studies covering the topic of the most common visuospatial neglect rehabilitation methods effectiveness in adult stroke patients. The following eligibility criteria were applied.

2.1 Search strategy

The literature search was conducted on Pub Med using the following MeSH term: ("visuospatial neglect"[Title/Abstract] OR "hemispatial neglect"[Title/Abstract] OR "unilateral spatial neglect"[Title/Abstract] OR "visual neglect"[Title/Abstract] OR "spatial inattention"[Title/Abstract]) AND ("stroke"[MeSH Terms] OR "stroke"[Title/Abstract] OR "post-stroke"[Title/Abstract] OR "cerebrovascular accident"[Title/Abstract]) AND ("rehabilitation"[MeSH Terms] OR "rehabilitation"[Title/Abstract] OR "therapy"[Title/Abstract] OR "treatment"[Title/Abstract] OR "intervention"[Title/Abstract]) AND ("prism adaptation"[Title/Abstract] OR "visual scanning training"[Title/Abstract] OR "virtual reality"[Title/Abstract] OR "neurostimulation"[Title/Abstract] OR "transcranial magnetic stimulation"[Title/Abstract] OR "TMS"[Title/Abstract] OR "transcranial direct current stimulation"[Title/Abstract] OR "tDCS"[Title/Abstract] OR "mirror therapy"[Title/Abstract] OR "robot-assisted therapy"[Title/Abstract] OR "sensory stimulation"[Title/Abstract] OR "limb activation"[Title/Abstract] OR "optokinetic stimulation"[Title/Abstract] OR "constraint-induced therapy"[Title/Abstract] OR "constraint-induced movement therapy"[Title/Abstract]) AND ("2015/01/01"[Date - Publication] : "2025/12/31"[Date - Publication]) AND ("humans"[MeSH Terms]) AND (English[lang]).
The search was supplemented by manual screening of reference lists of identified systematic reviews to capture any relevant studies not retrieved by primary search.

2.2 Eligibility criteria

Following eligibility criteria were applied for the studies.

The target population was comprised of adult humans experiencing visual spatial neglect resulting from stroke. Non-human subjects, pediatric population and studies not addressing visuospatial neglect as direct outcome of stroke were excluded.

Interventions included were prism adaptation, visual scanning training, virtual reality, robot assisted therapy, transcranial magnetic stimulation, transcranial direct current stimulation, sensory stimulation, limb activation therapy, optokinetic stimulation and constraint induced movement therapy. While initially planned, no eligible studies were identified for visual scanning training, sensory stimulation, limb activation therapy or constraint induced movement therapy therefore these were excluded as well. Other rehabilitation methods other than the ones mentioned before were excluded.

The designated outcomes comprised assessment of rehabilitation effectiveness in visuospatial neglect. For study design only peer-reviewed studies were eligible, including RCT, observational studies, systematic reviews, meta-analyses, and case reports with a sample size exceeding five participants. Non-peer-reviewed publications, editorials, opinion pieces, and case reports with fewer than five participants were excluded.

Only studies reporting available results were included, study protocols without results and review articles covering the similar or overlapping topics were excluded.

Only publication within the last 10 years were included therefore publication published before 1st January 2015 were excluded. Only English publication which were fully accessible via institutional access were eligible.

2.3 Study selection and data extraction

The results were screened in two stages. In the first stage titles, abstracts or summaries and accessibility were assessed against eligibility criteria and studies meeting obvious exclusion criteria were removed. In the second stage the texts of the remaining articles were reviewed in full. Studies in this phase were excluded if they did not meet population, intervention or outcome criteria, if only protocols without results were available or if they were identified as reviews covering the same topic. The selection process is visualized in the flow diagram Figure 1.

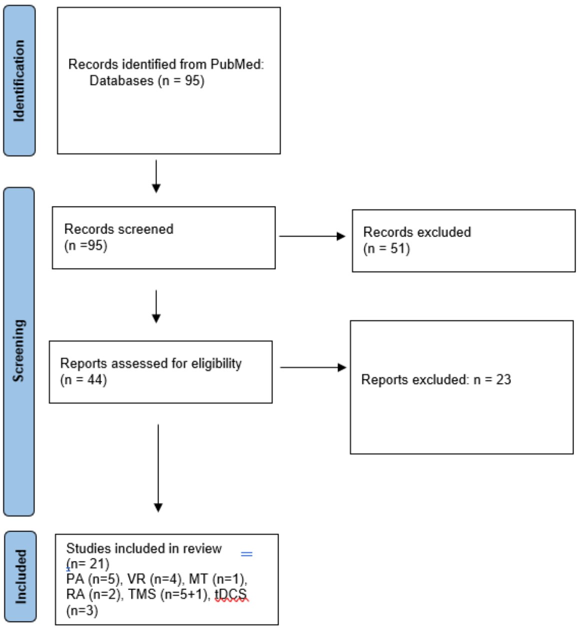

Figure 1: Flowchart

Data was extracted by the primary author, using a standardized extraction form capturing study type, design, sample size, clinical characteristics, intervention type, protocol parameters, outcome measures used and key finding concerning short- and long-term effectiveness. A narrative synthesis approach was adopted given the heterogeneity of interventions, outcome measures and study designs of included literature.

3 LITERATURE REVIEW

This literature review presents an analysis of peer-reviewed literature, examining the effectiveness across 6 different major USN rehabilitation methods including PA, VR assisted therapy, mirror therapy, robot assisted therapy and 2 modes of noninvasive brain stimulation (TMS and tDCS).

3.1 Prism adaptation

Prism adaptation (PA) is a visuomotor rehabilitation technique which uses the brains capacity for sensorimotor recalibration. During PA session the patient is seated and wears prismatic goggles that optically displace the entire visual field laterally. This displacement is usually 10-15° towards the ipsilateral side. While wearing these goggles the patient performs a series of repetitive tasks such as arm reaching or pointing movements directed towards visual targets presented at body midline or in the left or right hemisphere. A session usually lasts around 15-20 minutes and consists of 50-90 pointing movements (9,10).

There are two main hypotheses that could explain the mechanisms behind rightward PA improving left sided spatial neglect one is due to a shift of hemispheric dominance within the ventral attention networks post PA and the other is that spatial neglect represents a dysfunction in rapid calibration processes which occurs due to a reduction in workspace where spatial attention is allocated and PA represents a position adjustment of this task workspace which helps to translate between different sensory motor systems (11).

A meta-analysis by Orsolya Székely et al. regarding the topic of short-term treatment effects of prism adaptation for spatial neglect evaluated 16 studies with a total patient count of 430 patients across treatment and control groups. Primary improvements were evaluated with the help of BIT-C and cancellation tasks, while the secondary improvements were evaluated with CBS. Orsolya Székely et al. found that the current evidence does not support the routine usage of PA as a treatment option for spatial neglect. Their analysis found no statistically significant benefits in terms of short-term therapeutic benefits. Due to this limitation of short-term effect, the authors suggest it is highly unlikely that any positive changes in effectiveness would occur in later evaluation or in the long term. This leads Orsolya Székely et al. to question, if further resources should be committed to researching this topic despite the unclear nature of effectiveness of PA even after 25 years of researching this method. The authors mention that most studies included were at high risk of bias and used heterogeneous protocols. Additionally, they note that many of the studies require more participants to reliably detect modest treatment effects. All of which limits the strength of their conclusion. They mention the need for a more standardized approach for any further research in this topic, this would minimize the difficulty in quantitatively combining future data. (12)

An RCT by Antonia F Ten Brink et al. concerning PA effect on subacute phase post stroke came to similar results. This RCT included 69 patients from varying age groups, all with a clinical stroke diagnosis. These patients were split into 2 groups with one receiving PA and the other receiving SA for 2 weeks, in addition to the standard treatment. Their improvements were measured at baseline and in week 1-4, week 6 and week 14. Improvement of ADL was evaluated via CBS. Additionally, to CBS score subjects were evaluated by MAC at baseline and at week 2, 4 and 14 and SC was evaluated at the same frequency as CBS. When comparing improvements across these multiple evaluation tools, the authors found no significant difference between any of them. The researchers found an overall detectable improvement in the PA group. However, similar improvements could be seen in the SA group and when comparing the results between groups there was no statistically significant difference between the improvements detected in PA and SA at any point in time. The authors mark that the heterogeneity of the neglect symptoms and spontaneous recovery are major confounders impacting the results. Furthermore, the authors mention that it has been argued that SA could be considered a form of visuomotor training as well, due to the SA procedure requiring the patient to plan and perform a series of movements towards the ipsilateral and contralateral side, half of which might train the orientation of the sensorimotor system towards the side with the neglect. This could weaken the contrast between PA and SA. They additionally mention that several other studies showed a clear visible distinction between PA and SA, leading them to the conclusion that there might be other factors impacting the patients recovery and therefore explaining the differences in PA effectiveness. The authors note the heterogeneity of the participant potentially preventing the detection of more subtle effects of PA. (13)

A study by Marine Lunven et al. covering the anatomical predictors of a successful PA treatment reached a different conclusion. This study included 14 patients with a single side right hemisphere hemorrhagic or ischemic stroke. They further selected patients with chronic visual neglect and excluding strokes that occurred in the last 3 months before the study. The visual neglect severity was assessed by 6 paper and pencil tasks including, letter cancellation, the copying of linear drawing of a landscape, text reading, bisection of five 20cm horizontal lines, drawing from memory of a daisy and a landmark task. These were done 1 day before PA, 2 hours before PA and soon after PA. They found that the effectiveness of PA varies widely and that the effectiveness is influenced by the integrity of some brain structures. The interconnectivity of the left and right hemisphere, especially the interconnectivity of frontoparietal attention networks and the preservation of callosal pathways seems to be critical when it comes to compensation of neglect signs after a single PA session. Patients with damage to any of these structures showed an overall poorer response to PA. The authors mark that despite the limited amount of participant, their sample is representative of the general populations lesion patterns when it comes to chronic neglect patients. (14)

Jing Li et al. conducted a systematic review and meta-analysis covering the topic of effects of prism adaptation for USN post stroke. This paper included 8 RCT with a total patient population of 244. 130 of which were in the experimental group and 114 in the control group. Treatment effectiveness was confirmed with the CBS in three of them, behavioral inattention test in 6 of them, three of them using SCT, two of them used reading task, two of them used FIM scale and two of them line bisection test. The researchers found no significant change in CBS, when it came to FIM there were significant changes in 1 of the 2 studies using this method. When it came to BIT, SCT, RT and LBT all of them showed positive changes initially, but they either disappeared or were unclear in the long term. Overall Jing Li et al. concluded that PA had significant short-term effects on USN patients, but the long-term effects need to be further explored. They mark some limitations including sample size, some studies not clearly reporting the randomness and allocation concealment facilitating selection and performance bias, some studies were lost to follow-up facilitating detection bias and them focusing on English publications only. (15)

Another systematic review and meta-analysis by Yumene Naito et al. covering the topic of the short-term effects of PA treatment on the severity USN post right hemispheric stroke included another 7 RCT with a total of 227 participants. Across those RCT were measured using conventional neuropsychological assessment methods and functional outcomes were measured by CBS. The researchers came to the conclusion that PA showed significant short-term effects on primary outcome measures of USN, however they mark that the certainty of the evidence is low. Additionally, they emphasize that PA with angles past 10° yielded better results for both USN symptoms and improvement of activities of daily living. They further mention that these positive findings measured when using PA with more than 10° might be a factor explaining different conclusions regarding PA in previous studies, however this requires further research and future RCT should consider using larger PA angles and long term follow up for these patients. The authors mark some key limitations including Publication bias due to only using English sources, the limited amount of papers they included, some subgroups lacking data for analysis and them needing to use WebPlotDigitizer to extract data due to it being only represented within graphics and that most of the data they collected for their group and subgroup analyses had either low or very low certainty. (16)

Table 1 Prism adaptation overview

Source	Type	Short-term effectiveness	Long-term effectiveness	Limitations
(12)	Meta analysis	No significant benefit over SA or control	No effect	High risk of bias, heterogeneous protocols, limited participant numbers

*Source (12): long term effects are "highly unlikely" given the absence of short term effects → classified as no effect

Table 1 Prism adaptation overview (continuation)

Source	Type	Short-term effectiveness	Long-term effectiveness	Limitations
(13)	RCT	No significant difference between PA and SA at any point in time	Unclear	Heterogeneity of sample, spontaneous recovery as confounder, SA potentially acts a visuomotor training
(14)	Observational study	Lesion dependent, with poorer response when frontoparietal or callosal pathways are damaged	Not mentioned	Very small sample (n=14), single session of PA only, chronic neglect patients only
(15)	Systematic review and Meta analysis	Yes	Unclear	Limited sample size, risk of selection, performance and detection bias, Publication bias due to English only publications
(16)	Systematic review and Meta analysis	Yes	Unclear	Low certainty evidence, limited number of studies included, Publication bias due to English only publications, data extracted via WebPlotDigitizer in some studies

The studies regarding the effectiveness of prism adaptation present conflicting results regarding its effectiveness. This ranges from one meta-analysis and one RCT included finding a similar improvements in using PA and SA when comparing to control group (12,13) while 2 systematic reviews and meta-analysis find statistically significant benefits in using PA over control in the short term (15,16). When it comes to the long-term effectiveness of PA all sources agree regarding the uncertainty of it. These inconsistencies of finding might suggest that PA might produce temporary improvements which do not translate into long term functional recovery, another possibility is that as one of the studies mentioned it could be argued that SA could be considered as a form of visuomotor training as well due to it requiring the patient to perform plan and perform movements toward their ipsilateral site(13). The location of the lesion is likely to play an important role as well, Marine Lunven et al. found that the patient with an injury disrupting the interconnectivity between left and right hemisphere especially the frontoparietal attention networks and callosal pathways leads to a poorer response to PA (14). Another factor potentially explaining the differences in effectiveness is of PA across studies is the angle in which PA is applied, Yumene Naito et al. found that angles past 10° yielded better on USN symptoms and improvements of ADL when comparing to under 10°(16). Overall while positive effects could be observed in patients using PA it is not possible to conclude whether or not these positive effects are substantially more beneficial than the patient participating in SA.

3.1 Limitations

The research of PA is marked by the heterogeneity of data and small sample sizes available. Additionally the differences in prism angles, treatment duration, measurements of outcome and lack of follow ups and long term studies complicate statistical comparisons and make statements regarding effectiveness difficult to justify. (12,13,15,16)

3.2 VR rehabilitation

Virtual reality (VR) rehabilitation uses computer generated environments to deliver structured, controlled and repeatable spatial stimuli. VR systems used for neglect rehabilitation can be classified into 3 categories. Non-immersive VR (NIVR), semi-immersive VR (SIVR) and immersive VR (IVR), with NIVR using standard computer monitor or display screens and keyboards and mouse, gamepads or joysticks as a means to interact with the virtual environment, SIVR typically consists of a large screen on which the virtual environment is projection and using advanced interface devices such as haptic feedback devices as a means of interacting with the environment and lastly IVR which consist of a head mounted display and 3D input devices which allows for full VR immersion (17). Tasks delivered within VR can vary depending on system and can include tasks such as spatial search and exploration tasks, object recognition, virtual street crossing, catching or intercepting moving objects, simulation of activities of daily living such as kitchen tasks or navigating a room. Multimodal stimulation included auditory, proprioceptive and haptic cues alongside visual stimuli are used to further enhance spatial awareness and direct attention towards the neglected side(18,19)

VR systems have the potential advantage of overcoming the lack of specificity and sensitivity of pen and paper assessment tools however the heterogeneity of application is a major roadblock towards this goal at the moment (20). The mechanism of action seems to be similar to prism adaptation and VR seems to enhance general cognition, alertness and spatial cognition and the perceived sense of presence might have beneficial effects particularly when it comes spatial neglect (21).

An emerging field of rehabilitation is rehabilitation with the help of VR. A study by Germain Faity et al. was done to test potential viability in healthy people. It included ten healthy adults between the ages of 23 and 39. Each underwent treatment with different modalities comparing real prism adaptation compared with virtual ones. The participants underwent each method in a randomized order and with a minimum of 48 hours rest between each. Evaluation was done in 3 sets “the Real Set” with exposure to real conditions and real prisms, “the Mixed Set” with real conditions but exposure to virtual prisms and “the Virtual set” performed fully under virtual conditions. Tools to measure efficacy used were mSSA, vSSA, VOL and 80 or 100 pointing movements immediately after intervention and mSSA, vSSA and VOL two hours post intervention. The study came to the conclusion that rehabilitation procedures performed with real prism were not inferior compared to the virtual ones. Additionally, the authors highlight potential benefits including options for a more personalized rehabilitation program and making measurement process much easier and therefore enabling daily usage during the patients rehabilitation. The authors mark that further research on the targeted population is required. (22)

Another study by Ho-Suk Cho et al. tested practical application of VR rehabilitation on subacute stroke patients, specifically it included 24 individuals who had strokes 1-6 months before initiating therapy. Both groups underwent 12 sessions of standard USN treatment or VR USN treatment over a period of 4 weeks in addition to 5 weekly sessions of motor and neurodevelopmental training. Both were evaluated via LBT, CBS, MBI, MVPT-V and head tracking sensor data. The researchers came to the conclusion that the incorporation of VR is at least as effective as conventional methods and when using the LBT, mean MVPT-V changes and head tracking data improvements were significantly greater in the VR group. The authors mark that the results should be considered as preliminary data, due to the small scale at which the study was conducted. (23)

A systematic review by Adriana Salatino et al. covered the topic of VR rehabilitation. It specially emphasizes the differences between immersive, semi-immersive and non-immersive techniques. The review included 26 studies that covered the topics of VR rehabilitation for neglect in adults with USN after stroke. Inclusion criteria required presence of rehabilitative outcomes and the papers being published in English. Adriana Salatino et al. came to the conclusion that VR has the potential to be a future treatment method for USN regardless of immersion level, they suspect that the rehabilitation effectiveness might depend on the simulation itself rather than the level of immersion the patient experiences. The direct comparison of all three types of immersion was not directly possible due to the heterogeneity of data, but they mark that the level of immersion correlates to patients enjoyment which could play an important role in the success of recovery. Furthermore, the researchers mark some limitations of this paper, including the small number of RCT and class 1 studies, the lack of control groups in some sources, the lack of assessment of patients assessment of VR experience and the lack of heterogeneity due to different VR methods used. All of these factors should be considered and the researchers suggest further trials to be conducted in this field. (17)

A study by Katarzyna Matys-Popielska et al. regarding the possibility of incorporating VR application in the rehabilitation process of elderly stroke patients. They put special emphasis on potential complications arising from factors such as technological affinity. They included 60 individuals, 30 of which were post stroke patients. These 60 people were split into control and study group with the control group divided into 3 subgroups. The first subgroup had an average age of 21.3, the second subgroup had an average age of 53.1, the third subgroup had an average age of 76.5 and the fourth group had an average age of 72.83. The fourth group was comprised of individuals with previous ischemic strokes. After asking patients for their subjective self-assessment, regarding them being open to the incorporation of newer technologies into rehabilitation programs and whether or not they were satisfied with these forms of exercise after trying it. Group 1 was highly enthusiastic about VR applications and 100% wanted to try them. This was reduced to 90% in group 2 and 50% in group 3. Most people from these groups were able to perform rehabilitation tasks and 90% gave a positive evaluation after trying it out. In group 4 only 47% of patients wanted to try these new rehabilitation tools, with the rate becoming less the older the patients got, peaking at 25% in the 75-90 age group, however after initial skepticism 75% were happy with it afterwards. However, in group 4 the rate of people being able to fully perform the rehabilitation tasks was lower than in the comparison groups. While this could be interpreted as VR being less effective for older people or people with neurological disorders, the researchers came to the conclusion that the advanced age and presence of stroke itself does not negatively impact the patients ability to perform these tasks, its more about the general condition of the patient and additional factors such as contact with technology, physical condition, time since stroke occurred as well as personal ability and cognitive attainment. The impaired execution of VR tasks is similar to the execution of conventional rehabilitation tasks. Additionally, they conclude once the initial barrier of skepticism is broken in older people, VR rehabilitation is equally effective for the young and the elderly. The authors mention the further need for research regarding the effectiveness of VR on diverse patient groups with large sample sizes, as well as the need for long term studies. (24)

Table 2 VR therapy overview

Source	Type	Short-term effectiveness	Long-term effectiveness	Limitations
(22)	Validation study (healthy subjects)	No statistical difference between VR and real PA	Not mentioned	Healthy subjects only, small sample size (n=10)
(23)	RCT (pilot)	More effective than conventional	Not mentioned	Small sample size (n=24), preliminary data, single blind design
(17)	Systematic review	Positive effects across all immersions levels, effectiveness appears independent of immersion level	Not mentioned	Few high quality RCTs included, heterogeneity of VR systems and tasks, lack of control group in some included studies
(24)	Feasibility study	Feasibility confirmed across all ages, effectiveness of outcome not assessed	Not mentioned	Feasibility focus only, no effectiveness outcome data, mixed population of stroke and healthy participants, small subgroups

*Source (17) does not measure USN outcomes

VR based rehabilitation demonstrated statistically significant improvements on functional outcome measures including improvements in visuospatial performance and attentional tasks. One study found no statistically significant difference when comparing the use of VR prisms to regular PA (22). Another one reported statistically significant improvements in LBT, MVPT-V changes and head tracking data when comparing to conventional therapy (23). The effectiveness of VR seems independent to its level of immersion and seems to depend on the stimulation received through VR itself (17) The advantage of VR is that it provides a more interactive and engaging environment which could have an impact on the patients enjoyment of the rehabilitation process and as a consequence these increases to motivation might increase adherence towards the program. Regarding this point Adriana Salatino et al. mark an increase in immersion correlating to the patients enjoyment (17). There is also the potential for a highly individualized training program which might be able to enhance effectiveness and could be more accessible across a diverse patient population. A disadvantage might be the aversion of the elderly towards new and unfamiliar technologies and their inability to perform complex tasks within VR. This topic was covered in another study which evaluated feasibility of VR technology across multiple age groups and for stroke patients, Katarzyna Matys-Popielska et al. found that while there was an initial aversion towards the usage of VR which correlates with an increase in age, the execution of tasks and positive reception was similar amongst all age groups after going through the exercises. They also covered the topic of tasks being too complicated and came to the conclusion that presence of a stroke itself does not negatively impact the patients ability to perform these tasks. A decreased ability to follow the instructions is related to the general condition of the patient and additional factors such as contact with technology, physical condition, time since stroke occurred as well as personal ability and cognitive attainment. They mark that an impaired execution of VR tasks is similar to the impaired execution of conventional rehabilitation tasks (24).

3.2 Limitation

The evidence regarding VR assisted rehabilitation remains preliminary due to small sample sizes (23) and the limited number of high quality RCTs and no standardization across VR systems and their application (17). Furthermore, there is a lack of data concerning long-term viability.

3.3 Mirror therapy

Mirror therapy is a rehabilitation technique that uses visual feedback derived from a mirrors reflection of affected limb to modulate motor and attentional processes. During standard procedure the affected limb is placed inside a mirror box which inhibits patients ability to view this limb directly, the patient is then instructed to focus on the mirror which reflects the image of the healthy extremity creating the illusion that their affected limb moves normally (25,26). Each therapy session can incorporate movement oriented practice, including simple repetitive limb movements without object manipulation or task oriented practice involving the manipulation of common objects (26,27). This is thought due to mirror therapy being able to engage the damaged hemisphere demonstrated by Garry et al., they showed that viewing the reflection of unilateral hand movements facilitated excitability of the ipsilateral primary motor cortex (28) and Kexu Zhang et al. highlighting the role of mirror therapy in facilitating motor signal transmission via ipsilateral motor pathway towards affected limb (29).

Regarding mirror therapy only one study was included, in a systematic review by Thieme H et al.. This review was primarily focused on the aspect of motor function recovery using mirror therapy post stroke, however it puts a secondary focus on ADL, pain and visuospatial neglect. While the overall review included 62 studies and a total of 1982 participants, only five of them reported outcomes on visuospatial neglect. The combined sample size for those was 175 with 109 receiving treatment and 66 as control group. The authors overall conclusion was that while there is moderate evidence supporting the usefulness of mirror therapy for improving lower extremity function as well as improving activities of daily living, there is no statistically significant effect of mirror therapy compared to control group. They mention limitations to the amount of studies and participants and the low quality of evidence. (25)

Table 3 Mirror therapy overview

Source	Type	Short-term effectiveness	Long-term effectiveness	Limitations
(25)	Intervention review	No effect in USN compared to control	No effect	Very few studies reporting on USN outcomes (5 of 62), small, combined sample (n=175), low quality of evidence

*Source (25) long-term data was not reported separately but overall conclusion was that no effect is present

Mirror therapy did not demonstrate a statistically significant improvement within the USN subgroup (25). While it might be effective for motor recovery there is no reason for its application in USN rehabilitation.

3.3 Limitation

Limitations include small amounts of studies and low quality of data (25).

3.4 Robot assisted therapy

Robot assisted therapy encompasses the use of mechatronic devices to guide and assist upper or lower limb movements during rehabilitation. In the context of USN this primarily means aiding the affected limb in training on the ipsilateral side of neglect. Generally, two main categories of devices are used for rehabilitative purposes, these include End effector robots and exoskeleton robots. End effector robots are connected to patients at one distal point, usually the hand or wrist and their joint do not match the humans joints. They guide the patients movement through space generating trajectories in one or two planes. Exoskeleton robots on the other hand are worn across the full length of the extremity and provide joint by joint guidance allowing multiple degrees of freedom and resulting in a wider range of possible movements, mimicking natural movements more closely (30,31). Regardless of type of device used robotic devices provide highly repetitive task specific movements, mimicking conventional therapy with a physiotherapist but applying far greater repetitions and intensity (31,32). Neha Singh et al. propose that the highly repetitive and task specific movements of the affected limb might help the activation of ipsilesional hemisphere which could indicate reactivation of the lost neural circuits, unmasking of preexisting synapses, recruitment of perilesional areas in ipsilesional hemisphere or the exploitation of the preserved functional reservoir in ipsilesional hemisphere (33).

A study by Jin-Jyuck Park measured the effectiveness of robot assisted left hand training on hemispatial neglect. It included 24 chronic stroke patients with 12 in both control and treatment group, all patients were above 65 years, had a right hemispheric stroke confirmed via CT or MRI, had only a singular stroke, their global cognitive function was confirmed via Korean version of Mini Mental State Examination (MMSE) with a score >24, the stroke occurred more than 6 months ago and the presence of neglect was confirmed via line bisection test and Korean version of MVPT-3. Participants took part in 20 sessions over 4 weeks, each consisting of 30 minutes of training, 15 minutes focusing on grasp and release training and 15 minutes focusing on count training. The control group received 20 sessions of conventional treatment. Results were evaluated using the LBT, the Albert´s Test and CBS. While there was an overall improvement in both groups, the group using robot assisted left hand training had a statistically significant improvement in all 3 categories when comparing to conventional treatment. The author notes that his results still have some limitations due to the small sample size of 24 patients, the lack of long-term observation and lastly the lack of neuroimaging post treatment to confirm the extent of right hemispheric activation. He emphasizes that further research should include functional magnetic resonance imaging to confirm the neuronal changes of robot assisted left hand training in hemispatial neglect patients. (34)

A systematic review and meta-analysis by Rodrigo Bazan et al. covered the topic of robot assisted trainings effect on USN post stroke. The researchers included 5 studies with a total of 73 in the intervention and 69 in the control group in their systematic review, 4 of which were included in their meta-analysis. Evaluation occurred with the help of a multitude of tests including the Motor-Free visual perception test third edition (MVPT-3), the line bisection test (LBT), the star cancellation test (SCT), the Alberts test (AT) and lastly the Catherine Bergego Scale (CBS). While the Data showed a statistically significant improvement in the LBT, when assessing visual scanning, functionality and ADL via MVPT-3, SCT, AT and CBS they found no change in effectiveness compared to the control groups. The authors mark that the quality of evidence available from 2 of the sources was low and the limited sample size of RCT´s included. (35)

Table 4 Robot assisted therapy overview

Source	Type	Short-term effectiveness	Long-term effectiveness	Limitations
(34)	RCT (pilot)	Significant improvement over conventional treatment	Not mentioned	Small sample size (n=24), no long term follow ups, no post treatment neuroimaging to confirm neuronal changes
(35)	Systematic review and Meta analysis	Task specific improvement, improvement on LBT, no significant difference on MVPT-3, SCT, Alberts test or CBS	Not mentioned	Mixed quality of evidence with some of the evidence being included being of low quality, small RCT sample sizes, heterogeneity of robotic system and protocols

Robot assisted therapy shows statistically significant improvements in specific tasks such as line bisection (34,35) their translation towards improved, visual scanning and ADL is uncertain. A small scale study by Jin-Jyuck Park found an across the boards improvements of spatial perception, visual scanning and functional improvement of ADL when comparing to standard intervention (34). A systematic review and meta-analysis by Rodrigo Bazan et al. came to a similar conclusion when assessing spatial perception via the line bisection test. However they did not find any significant improvement in visual scanning and functional improvement of ADL (35). These findings suggest that robot assisted therapy might be effective for task specific rehabilitation but might not generalize to broader functional outcomes such as assessed by CBS.

3.4 Limitations

Limitations include small sample size (34,35), overall low quality of RCTs and heterogeneity of robot systems and protocols (35), lack of long term follow up and functional MRI data (34).

3.5 Noninvasive brain stimulation

A systematic review and meta-analysis by Flavio Taira Kasiwagi et al. covered the topic of effectiveness of noninvasive brain stimulation, further examining transcranial direct current stimulation, repetitive transcranial magnetic stimulation and theta burst stimulation. The review overall included twelve RCT with a total of 273 participants and 4 non RCT with a total of 94 participants for qualitative synthesis, with 8 of them covering the topic of cTBS, seven of them covering tDCS and the remaining 3 covering rTMS. Out of these 16 studies six RCTs with a total of 116 participants were included in quantitative analysis. The included trials used varying combinations of Star Cancellation Test, line bisection test, motor-free visual perception test, Alberts test, line crossing test or measured outcomes in other ways such as impact on ADL or occurrence of adverse events. Based on the data from those 6 RCT researchers came to the conclusion that overall there is a beneficial effect when using noninvasive brain stimulation for USN, they found significant differences when using noninvasive brain stimulation over sham treatment when assessing with line bisection test, motor free visual perception test, Alberts test and line crossing test. However, when assessed with the Star Cancellation Test no significant differences were observed. To conclude they found moderate quality evidence that rTMS at 1 Hz is more efficacious than sham and low-quality evidence when assessed by motor free visual perception test. There was low quality evidence that noninvasive brain stimulation particularly rTMS is overall beneficial for USN when measured by line bisection test, Alberts test or line crossing test. However Flavio Taira Kasiwagi et al. mark limitations including substantial selection bias, unblinding, an overall lack of the number of participants included and an overall small amount of trials. (36)

Table 5 Noninvasive brain stimulation overview

Source	Type	Short-term effectiveness	Long-term effectiveness	Limitations
(36)	Systematic review and Meta analysis	Yes, moderate quality for rTMS at 1HZ compared to SA, low quality evidence for other NIBS modalities	Not mentioned	Substantial selection bias, unblinding risk, limited number of participants and trials included, heterogeneity across NIBS modalities

3.5.1 Transcranial magnetic stimulation

Transcranial magnetic stimulation is a noninvasive neuromodulation technique that uses rapidly alternating magnetic fields to induce electrical currents within cortical neurons, modulating their excitability in a frequency dependent polarity equivalent manner. During the sessions a conducting coil is held against the patient scalp over the targeted cortical region and electrical current pulses through the coil generating a magnetic field that can penetrate the skull and leads to localized depolarization within the cortex. Repetitive application is termed repetitive transcranial magnetic stimulation (rTMS) (37). The effect on the underlying tissue varies with frequency with high frequency stimulation (≥1 mainly 5-20Hz) enhancing cortical excitability and low frequency (≤1Hz) suppressing it. Additionally these effects seem to persist beyond the duration of the TMS application (38–40). Currently there are 2 main approaches towards application in USN first inhibitory low frequency rTMS (typically around 1 Hz) that is applied to the contralesional posterior parietal cortex and high frequency rTMS (typically 10-20 Hz) applied to ipsilesional posterior parietal cortex (39,41). A variation of regular protocol is theta burst stimulation which consist of three short repetitive high frequency TMS at 30-100 Hz in the theta frequency range (4-7Hz) this pattern may either be used excitatory as intermittent theta burst (iTBS) or inhibitory as continuous theta burst (cTBS) (38). The main theory behind TMS application is grounded in the interhemispheric rivalry, competition or inhibition model which describes the both parietal cortices as exerting reciprocal interhemispheric inhibition, which is disrupted post stroke leading to the damaged side exerting less inhibition and therefore disinhibition of the unaffected side which causes further suppression of the affected side (37–39,41,42).

A systematic review by Jeannette Hofmeijer et al. covered 57 trials with a total of 2595 subjects. While not specifically focusing on the aspect of spatial neglect they evaluated subjects with the international classification of functioning, disability and health focusing on outcome measures at the level of body and the level of activities. Jeannette Hofmeijer et al. performed subgroup analysis according to the type of rTMS performed including low frequency rTMS, high frequency rTMS, intermittent theta burst stimulation iTBS, paired associative stimulation, transcranial rotating permanent magnet stimulation, short inter train interval ITI rTMS and long ITI TMS. Additionally, they separated the timing of treatment into withing 3 months of stroke and at 3 months or later after stroke onset. The authors came to the conclusion that there is some evidence supporting efficacy on upper limb synergies, muscle strength global cognitive function and most importantly visual/spatial inattention, these positive effects are not reserved to a specific subgroup and no differences can be observed between any of the different treatment methods or time of intervention. The authors mark that this evidence is challenged due to unexplained heterogeneity across many small sampled trials and they recommend larger scale trials with standardized treatment protocols and outcome measurement and a more rigorous collection of patient data concerning the topics of baseline severity of neurological deficit, imaging of the size and location of affected brain areas and data on the spared brain networks integrity to obtain more data and enable better subgroup analysis. (43)

A systematic review and meta-analysis by Tingting Jiang et al. cover the topic of theta burst stimulations role in stroke rehabilitation and includes 33 RCTs. While the majority of them cover other stroke symptoms 8 of them, translating to a total of 144 patients, specifically covers the topic of visuospatial neglect. Tingting Jiang et al. came to the conclusion that there is an overall positive effect on the functional impairment when using TBS in rehabilitation. For visuospatial neglect specifically the authors suggest that continuous TBS (cTBS) of left hemisphere posterior parietal cortex (LH PPC) is effective for acute and subacute stroke patients. Furthermore, they mark that the modified cTBS protocol (801 pulses) seems more effective than the standard 600 pulse stimulation. However, Tingting Jiang et al. mention the low quality of evidence due to risk of bias and inconsistencies across data in addition to the small sample size of data and potential publication bias due to them only using English studies. They mark that further research should be conducted evaluating the effect of factors such as age, severity of injury, type of injury and adjuvant therapy have of TBS. (44)

A meta-analysis by Ruixuan Lin et al. concerning the topic of improvement of USN symptoms post stroke after receiving rTMS included another 16 studies. Treatment efficacy was evaluated by line

bisection test, CBS and Star Cancellation Test or Cancelation subtest. Authors came to the conclusion that overall rTMS had statistically significant effect in USN improvement and improvement in daily activities when compared to control group, furthermore they mark that excitatory rTMS of the ipsilateral hemisphere might seem to be more effective in rehabilitation compared to inhibitory rTMS of the contralateral side. They suggest that timing plays an important role in effectiveness of TMS with patients receiving treatment within the first 3 months post stroke benefiting the most. Ruixuan Lin et al. additionally mark that due to varied treatment duration, different target points, different frequencies use and overall differences in data extracted from studies resulting in heterogeneity of data combined with the lack of information regarding factors such as lesion location, types of USN and risk of publication bias, while still strong certainty of data was downgraded and further large scale studies in this field should be performed. (45)
An RCT by Wei Fu et al. investigated the long-term effects of cTBS in visuospatial neglect patients. The RCT included 20 patients in total, 10 receiving cTBS and 10 sham treatment. All patients were right-handed, had a stroke in their right hemisphere and suffered from visuospatial neglect. They received treatment for 14 consecutive days and were evaluated by SCT and LBT 1 hour before the first session, at the end of stimulation and 4 weeks post treatment. Researchers came to the conclusion that cTBS treatment over the left PPC in combination with conventional treatment resulted in significant improvement compared to sham group, this improvement lasted more than the 4 weeks after cTBS discontinuation, additionally significant improvement was observed even in the 4 weeks post cTBS which was not visible in sham group. Authors are also led to believe that the increased frequency of stimulations days and number of trains per day have compared with similar studies have a positive impact on the long-term benefits patients receive from cTBS. The authors mark limitations in stratification of patient age, lesion location or subtype of neglect and the exclusion of patients with visual fields defects which might lead to less severe patients being included. (46)

An RCT by Yong Kyun Kim et al. was done to evaluate the effectiveness of multiple stimulation sessions of rTMS. The RCT evaluated 34 patients, 19 of which received a single session of rTMS and 15 who received daily session for 2 weeks for a total of 10 sessions. Results were evaluated by letter cancellation test, line bisection test and Ota`s task. Then baseline performance in groups 1 and 2 was similar and the effects after the first stimulation were the same. Differences became visible after 1 group received 9 additional sessions of rTMS and an improvement across letter cancellation test, line bisection test and Ota`s task could be observed when comparing to control group. Researchers came to the conclusion that the group with the 10 sessions showed better results, indicating that repeated sessions of rTMS have greater effect than a single one. Authors however mark that further research with a larger sample size and long term follow ups should be performed. (47)

Table 6 Transcranial magnetic stimulation overview

Source	Type	Short-term effectiveness	Long-term effectiveness	Limitations
(43)	Systematic review	Yes, positive effect on visuospatial attention with no difference between rTMS modalities or timing of intervention	Unclear	Unexplained heterogeneity of data across trials, sample size trials, lack of standardized protocols, insufficient patient data on lesion location, severity of insult, spared network integrity
(44)	Systematic review	Yes, especially cTBS over left hemisphere PPC in acute and subacute stroke, modified 801 pulse protocol appears to be superior to standard 600 pulse protocol	Unclear	Low quality evidence, risk of bias, inconsistencies across data, small sample, Publication bias due to English only publications

Table 6 Transcranial magnetic stimulation overview (continuation)

Source	Type	Short-term effectiveness	Long-term effectiveness	Limitations
(45)	Meta analysis	Yes, significant improvement in USN and ADL, excitatory rTMS of ipsilateral site appear to be superior to inhibitory rTMS of contralateral site, greatest effect appears to be within 3 months of stroke	Unclear	Data heterogeneity, publication bias, limited sample size, insufficient reporting of lesion location and USN subtype
(46)	RCT	Yes, significant improvement over SA	Yes	No Patient stratification for age, lesion location or neglect subtype, small sample (n=20), exclusion of patient with visual field defects
(47)	RCT	Yes 10 sessions of rTMS were significantly superior to a single session	Unclear	Small sample size (n=34), no long term follow up

*Source (46) positive effects persist beyond 4 weeks and further improved in some participants

TMS represents the most thoroughly studied approach covered in this review. A large systematic review including over 57 individual trials with a total participant count of 2595 reported significant improvement in visuospatial inattention, cognitive and motor function. While this review wasn’t primarily focused on USN, subgroup analysis found that these improvements coexisted amongst all groups (43). Similarly, positive results were found in another meta-analysis, primarily focusing on USN, which found improvements in LBT and ADL when comparing participants receiving rTMS and control group (45) and a systematic review and meta-analysis which found low to moderate quality evidence that rTMS is more effective than SA particularly if applied at 1 Hz (36).

RCTs included support these findings as well, they found improvements in letter cancelation test, LBT and Otas task (47) and SCT and LBT(46). TBS a specific application of TMS also seems to be equally as effective. A systematic review concerning TBS usage as a rehabilitation tool for stroke did subgroup analysis for USN, while the certainty of evidence was described as low a positive trend could be observed, this seemed especially pronounced when applying modified cTBS protocol with 801 pulses over the left hemisphere posterior parietal cortex (44). Currently there seems to be unclear data concerning the effectiveness of which type of TMS to use with Jeanette Hofmeijer et al. finding no difference in effectiveness across a multitude of modalities including low frequency rTMS, high frequency rTMS, intermittent theta burst stimulation iTBS, paired associative stimulation, transcranial rotating permanent magnet stimulation, short inter train interval ITI rTMS and long ITI TMS (43) while Tingting Jiang et al. found that a change in the pulse frequency from the standard 600 to 801 would lead to an increase in effectiveness of cTBS (44). Additional important factors for the extent of positive effect seem to be location, frequency of application and timing of application (36,45–47). Ruixuan Lin et al. came to the conclusion that excitatory rTMS on the ipsilateral side seems to be more effective for rehabilitation than inhibitory rTMS on the contralateral site. They also found that patients that received rTMS within 3 months of stroke were the ones benefiting the most from the treatment (45), this might suggest heightened neuroplasticity during this time period. Repeated application also seems to have beneficial effects as Wei Fu et al. and Yong Kyun Kim et al. found that repeated application of cTBS and rTMS is beneficial compared to single a session (46,47), this might be explained due to cumulative neuroplastic changes. Important to mention is also that while no studies over truly extended periods of time are available, Wei Fu et al. found that while cTBS had a initial positive effect after the session, these effects did not only persist after reevaluation after 4 weeks but even further increased in some of their participants (46), this might suggest that cTBS has more long lasting effect than other modalities, increasing its overall clinical usefulness. In direct comparison of rTMS to other noninvasive brain stimulation modalities, rTMS seems to outperform as well suggesting it might be more effective in neuromodulation in comparison to e.g. tDCS (36).

3.5.1 Limitations

Despite the overall robust evidence some limitations have to be mentioned. This included substantial heterogeneity in stimulation protocols with varying frequencies, intensities, target regions and treatment durations. Additionally, many studies lack reporting of patients data concerning lesion location and severity, patient age, neglect subtype, adjuvant therapy used and integrity of spared neuronal networks. There is also a Publication bias with studies only relying on

English data (43–45). Also larger sample sizes (36,43–47) and long term follow ups (43–45,47) are required for more robust evidence.

3.5.2 Transcranial direct current stimulation

Transcranial direct current stimulation is a noninvasive neuromodulation technique that applies a weak but constant current to the cortex via electrodes placed directly on the scalp. Conventional tDCS setups consist of two surface electrodes, an anode and a cathode. They usually apply current in the intensity around 1-2mA. The current direction is determined by electrode polarity resulting in the current flowing from the anode to the cathode passing through both the scalp surface and the underlying cortical regions, inducing opposite effects at both electrode sites (48,49). The physiological effect of tDCS is polarity dependent with the anodal stimulation resulting in neuronal depolarization leading to neuronal excitability while cathodal stimulation results in a decrease in cerebral excitability (48). Application in stroke rehabilitation might vary but generally 3 options could be considered. First anodal stimulation with the anode placed over the ipsilesional hemisphere and the cathode placed over a neutral reference site such as the contralateral supraorbital area, this aims to increase the excitability of the damaged hemisphere. Second cathodal stimulation with the cathode placed over the contralesional hemisphere and the anode placed over a neutral reference site such as the contralateral supraorbital area, this aims to reduce activity of contralesional hemisphere. Lastly bi-hemispheric stimulation with anodal stimulation applied to ipsilesional hemisphere and cathodal stimulation applied to contralesional hemisphere, resulting in a reduced activity of healthy hemisphere and an increased excitability in ipsilesional hemisphere (50,51). The main theory behind the mechanism of tDCS is the same as for TMS the interhemispheric rivalry, competition or inhibition model (52).

An RCT by Michael Andres et al. included a total of 36 participants with no neurological deficit and required them to not have taken any neuromodulating drugs. The goal of the study was to evaluate the effect of bilateral tDCS on attention modulation which could be used as a foundation for neurorehabilitation in actual patients. Overall, the participants were involved in 1 pretreatment session followed by 3 tDCS sessions and one post treatment session after 24 hours, totaling 5 days overall. Results were evaluated via visual trials during tDCS. The researchers came to the conclusion that tDCS has the potential to improve visuospatial neglect in patients, they suspect that the overall effectiveness lies in the enhancement of attention control capacities by increasing visual sensitivity to peripheral targets. (53)

A systematic review by Elsner B Kugler et al. covered the overall effectiveness of tDCS on improvement of activities of daily living, physical and cognitive functions in post stroke patients. Overall, this review covered 67 studies with a total of 1729 participants. The effect on the secondary outcome USN however was only covered sparsely. In the end only one trial with 30 participants could be included in the analysis. Additionally, the researchers classified the data included from the trial as very low quality. This study reported improvement in neglect symptoms post tDCS. The authors came to the conclusion that further large scale randomized trials with parallel group design and sample size estimation are required to evaluate tDCS effectiveness. They mark study limitations including heterogeneous trial designs, high risk of bias and imprecision of effect estimates. (54)

A systematic review by B. Gonzalez-Rodriguez et al. Covering the topic of tDCS in neglect rehabilitation included 11 studies with a total of 152 participants. Participants received a variety of stimuli varying in electrode positions (unilateral or bilateral), intensity, electrode size, electrode density, number and duration of treatment, different tDCS devices and tDCS alone or in combination with other interventions throughout different studies. The authors came to the conclusion that there is moderate evidence for the usage of tDCS for USN rehabilitation. From available data dual stimulation seems to be more effective. However, the authors mark that, the current level of evidence makes it impossible to draw a categorical conclusion due to the limited number of studies, specifically in regards to benefits during acute, subacute and chronic phase of stroke in addition to the lack of long-term follow ups. They note that the heterogeneity in terms of methodology and clinically relevant factors. They mention the possibility of negatively polarizing data not being published due to publication bias. Additionally, there was also a huge difference in the quality of evidence included. (51)

Table 7 Transcranial direct current stimulation overview

Source	Type	Short-term effectiveness	Long-term effectiveness	Limitations
(53)	RCT (healthy subjects)	Yes, bilateral tDCS improved visual attention in healthy subjects, not tested in stroke patients	Not mentioned	Nonaffected population only, no post session follow up, questionable applicability to stroke patients

Table 7 Transcranial direct current stimulation overview (continuation)

Source	Type	Short-term effectiveness	Long-term effectiveness	Limitations
(54)	Systematic review	Unclear, only one eligible trial reported on USN and was classified as very low quality of evidence	Not mentioned	One eligible trial for USN, very low quality evidence, no long term follow up
(51)	Systematic review	Yes, moderate quality evidence for USN rehabilitation, bilateral stimulation appears to be superior to unilateral	Unclear	Methodological heterogeneity including electrode position, intensity, session number and devices used, varying quality of evidence, publication bias, small sample size, lack of long term follow ups

When comparing tDCS to other noninvasive brain stimulation such as TMS overall statistical evidence concerning effectiveness of tDCS is less robust. With a systematic review including over 67 studies only being able to include one which specifically addressed the topic of USN. While this one study was showing some benefit the overall quality of evidence was low (54). Another systematic review including 11 studies with 152 participants reported moderate evidence supporting tDCS effectiveness, especially when applying dual stimulation, a definitive statement regarding effectiveness here was not possible as well due to marked limitations (51). An RCT with 36 participants evaluating the effect on participants with no neurological deficit found the potential to improve visuospatial neglect in patients (53). tDCS is believed to enhance attention control mechanisms through the modulation of neuronal excitability and by increasing the sensitivity to stimuli in the neglected visual field (53). Therefore, bilateral stimulation might help rebalance hemispheric activity overall, exhibiting a similar mechanism to TMS. Findings in this field should be considered preliminary due to limited amount of evidence and overall lack of quality evidence.

3.5.2 Limitations

Key limitations include small sample size, heterogeneity in stimulation protocols, lack of long term follow ups and overall lack of data in this field. Statistical analysis is additionally impeded due to heterogeneity in study design. (51,54)

4 RESEARCH RESULTS AND DISCUSSION

When comparing the most commonly used and researched methods for USN rehabilitation Prism adaptation (PA), virtual reality based therapy (VR), mirror therapy, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) a number of important differences emerge regarding their consistency of evidence, patient suitability and overall effectiveness.

The evidence for PA is highly mixed with some finding short term benefits and inconsistent long-term benefits. PA appears to lack data confirming its therapeutic effect.
Evidence regarding the effectiveness of VR based rehabilitation is promising but preliminary and lacking in size. One small scale study indicates that it is at least as useful as conventional therapy and highlights the potential of a more personalized and motivating experience. However, studies included, include small sample sizes or nontarget population samples, heterogeneous VR system and lack long term follow ups. All of which makes the assessment of effectiveness difficult.
Mirror therapy shows some promise when it comes to motor recovery, however it shows no significant effect on USN across the available studies. However, the certainty of evidence is low here as well due to limited amounts of data and small population samples.
Robot assisted therapy shows selective effectiveness, with improvements being observed in the line bisection test, however these positive results fall short in consistency when it comes to tests assessing visual scanning and functional improvement in ADL. This might suggest that Robot assisted therapy selectively improves parts of spatial processing rather than the neglect itself.
Across the multitude of modalities, the noninvasive brain stimulations TMS and tDCS demonstrate the overall most positive and consistent effect for improving USN symptoms. While the data is limited by small sample sizes and heterogeneity the metanalyses consistently report statistically significant short-term benefits in visuospatial outcomes, with some even reporting these findings persisting for longer time periods. However, all of these also highlight substantial variability in stimulation parameters, lesion types, study design and assessment tools which limit the strength of this conclusion.

PA shows some improvement in visual tasks, but these rarely translate into functional changes in the CBS and ADL, additionally the effects diminish over time. VR rehabilitation tools show potential across both visuospatial and functional outcomes, however evidence should be considered as preliminary. Mirror therapy shows no significant impact on USN symptoms. Robot assisted training shows a consistent effect on line bisection test, but shows limited effect on broader neglect symptoms. TMS and cTBS produce improvements across multiple assessment tools including LBT, SCT and ADL. Some evidence suggests that repeated or higher frequency stimulation results in these effects remaining for longer. tDCS shows milder evidence of improvement. This might be especially true, when using bilateral stimulation. However, assessment of the magnitude of effect is uncertain due to the heterogeneity of stimulation protocols.
The difference between the effectiveness of these techniques might suggest that techniques like TMS and tDCS which directly modulate neural networks involved in spatial attention are more effective than interventions like PA which relies on sensorimotor recalibration or methods like VR, robotic or mirror therapy which have a task based approach.

There seems to be a variety of individual patient factors impacting the effectiveness of specific treatment methods. PA effectiveness seems to depend heavily on the lesions location, interhemispheric connectivity remaining intact. Suggesting that it might only be applicable to patients in whom these structural pathways remain intact. VR rehabilitation seems to be heavily dependent on the patients technological affinity and their overall physical condition and might require consultation especially for older people who might be skeptical regarding the rehabilitation method. Neuromodulation techniques seem much more suited to be applied in the acute or subacute phase of stroke, showing significantly better results in the first 3 months post stroke.

From a practical viewpoint VR and robotic therapy requires specialized equipment which can provide a personalized rehabilitation for patients. This equipment might not be affordable or available everywhere, however it has the advantage of requiring little medical oversight while performing the tasks. On the other hand, neuromodulatory interventions require medical equipment as well as trained operators and medical supervision. It has the advantage of only taking little time to show beneficial effects. PA is simple, inexpensive and easy to deliver, however inconsistency of effectiveness raises questions regarding its clinical usage. Mirror therapy is similarly inexpensive and easy to implement but currently there is no evidence of effectiveness, so clinical usage would not be reasonable.

When it comes to long term efficacy TMS and cTBS have the strongest evidence for sustained improvement which persists for longer periods of time, however even here further research is required. tDCS long term effects are uncertain due to a lack of follow up data. A similar lack of long term follow up data exists for VR and robotic therapy. The very little follow up data for PA suggests a limited long-term effect, however there exists a limited amount of evidence similar to tDCS, VR and robotic therapy. Mirror therapy shows no positive effect in long or short term.

Overall, the evidence for USN rehabilitation could be summarized as promising but heterogeneous research, with no modality supported by high certainty evidence and a critical lack of long-term effectiveness research. Out of all the modalities TMS currently shows the strongest methodological footing and the most consistency in clinical implementation, despite this evidence is still limited, especially concerning long term effectiveness. VR and robotics offer innovative personalized treatment but require more rigorous and standardized trials to evaluate their efficacy. PA suffers from inconsistent and mirror therapy insufficient evidence which raises questions if further resources should be allocated to researching them. tDCS shows some promise but there is a lack of high quality evidence.

Table 8 Conclusion summary

Intervention	Source	Evidence strength	Short term effectiveness	Long term Effectiveness	Functional impact (ADL)
Prism adaptation	(12–16)	Low	Mixed	Unclear	Minimal/ None
VR assisted Rehabilitation	(17,22–24)	Low/ Moderate	Low /Moderate	Not mentioned	Limited evidence
Mirror Therapy	(25)	Low	No effect	No effect	None
Robot assisted Therapy	(34,35)	Low	Task specific	Not mentioned	Inconsistent
TMS/cTBS	(36,43–47)	Moderate	Strong	Low /Moderate	Moderate
tDCS	(51,53,54)	Low/ Moderate	Low /Moderate	Unclear	Limited evidence

4.1 Limitations

When examining the available literature, a substantial variability in methodological rigor, sample characteristics, interventions protocols and outcome measures can be observed. The combination of these factors not only complicates the interpretation of individual findings, they also make comparison across modalities very difficult. The predominant limitations across all the different intervention types are small sample sizes, inadequate randomization procedures and insufficient blinding resulting in high Risk of Bias, heterogeneity of studies and lack of long term follow up all of which lowering the certainty of evidence.

The most predominant issue is the small sample sizes, resulting in low statistical power. This issue is prevalent throughout the different interventions and results in a reduced ability to detect true effect and greater susceptibility to exaggerated effect sizes.

One of the major challenges is comparison and statistical analysis is the heterogeneity of intervention protocols. This includes different stimulation frequencies, sites and pulse count in TMS and TBS studies, different electrode placement, intensity and session duration in tDCS, different prism angles, number of sessions and adaptation paradigms in PA, different types of VR systems varying in immersion level, interface and task design, different variations in robotic devices with different degrees of freedom and different training tasks. This heterogeneity complicates identifying optimal treatment parameters and contributes to the inconsistency of outcomes.

Another significant limitation for intercomparison lies in the heterogeneity of patient population. There is a huge variability in the lesions location and size, differentiation between ischemic and hemorrhagic strokes is made, timing of the stroke, severity and phenotype of USN, presence of cognitive or motor comorbidities. Many of the studies do not stratify or adjust for these factors. For instance, PA seems to be more beneficial if interhemispheric pathways remain intact and TMS seem to be the most effective within the first 3 months, consequently failure to account for these variables limits interpretability and might obscure meaningful subgroup effects.

Most studies rely on conventional paper and pencil tests including Line Bisection test, Cancellation Tests and Alberts Test which are sensitive but may lack ecological validity. Functional assessments like the Catherine Bergego Scale are used less frequently though they provide a much better picture of the ADL improvements. The usage of different combinations of assessment tools additionally complicates statistical analysis between different RCT´s. Additionally in some of the studies some improvements observed in laboratory tests fail to translate into improvements of ADL which raises the question of usefulness in clinical practice, this especially applies to PA and robot assisted therapy.

A recurring issue amongst all modalities is the absence of long-term follow ups. Most of the RCT´s evaluate outcomes immediately post intervention with only a handful of them assessing effects after multiple weeks. As a result, the duration of treatment effects remains unclear, while this issue is less prevalent for TMS and cTBS, there is almost no data for long term improvements in PA, VR, robotics and tDCS. This focus on short term effect makes it almost impossible to determine whether the improvements observed are signs of neuroplastic changes or a temporary compensatory effect. A frequent issue reported in Systematic reviews and meta-analysis is missing or incomplete methodological reporting in the RCT´s, a high or unclear risk of performance and detection bias due to a lack of blinding and the small studies effect contributing to publication bias. Given the novelty of technologies such as VR and robotics there is the chance of positive findings being overrepresented in literature. Especially when it comes to pilot studies that heavily rely on exploratory analysis. Lastly translating the findings into clinical practice remains limited due to a variety of issues. VR, robotics and TMS require specialized equipment which comes with a cost and might not be accessible to all hospitals. TMS and tDCS require personnel to receive specialized equipment training. There seems to be varying tolerability and acceptance when it comes to new technologies such as VR which can complicate clinical application. Due to the heterogeneity of treatment protocols, it is difficult to assess which of the approaches used should be implemented. Especially notable here is that the more simple and cheaper techniques PA and mirror therapy seem to be less effective which weakens their appeal for clinical usage, while the techniques with more robust evidence, namely TMS requires substantial infrastructure, impeding widespread implementation.

4.2 Research recommendations

The current body of research on the efficacy of Visuospatial Neglect Rehabilitation Techniques provides valuable foundational insight but ultimately remains inconclusive due to methodological heterogeneity, small sample size trials and limited long term follow ups. Several key areas covered require further attention to inform evidence based clinical practice.

Most of the studies included, including the ones covering PA, VR and robot assisted therapy, TMS and tDCS are limited by the small sample size or single center recruitment of RCTS conducted. To increase statistical power and allow a more thorough subgroup analysis e.g. by lesion location, neglect subtype or a comparison of acute, subacute and chronic, as well as improving the overall clinical applicability across a diverse general population, large multicenter trials are required. These would enable a more robust comparison in clinical effectiveness across a multitude of therapeutic approaches and would help to establish standardized clinical recommendations.

The heterogeneity of intervention protocols is a major barrier when it comes to cross study comparison and statistical analysis. Therefore, future research should prioritize the development of standardized treatment protocols. For TMS and TBS these should include consistent frequency, pulse number and target site. For tDCS these should include uniform electrode placement, intensity and session duration. For PA these should include the same prism angles and adaptation paradigms. For VR and robotic assisted therapy these should include standardized tasks. Minimizing heterogeneity would enable more meaningful meta-analysis.

Almost all studies included only focused on short-term effectiveness, leaving little information regarding the long-term efficacy of these therapeutic approaches. To determine their long-term viability and their clinical viability long term follow ups should be conducted. These should have follow ups of at least 3-6 months and should have repeated outcome assessments to track and quantify the maintenance or decay of therapeutic effects. Additionally, evaluation whether or not neural changes persist beyond initial recovery would be welcome. These long-term follow ups are especially critical for neuromodulation techniques where cumulative or lasting effects are plausible but insufficiently documented.

The overall evaluation of effectiveness of treatment suffers from similar problems as the Intervention protocols. There is a heterogeneity in evaluation tools used to assess improvements. Additionally, improvements in paper and pencil tests such as the line bisection test, do not necessarily translate into actual improvement in ADL. Therefore, future studies should include functional assessment tools such as the Catherine Bergego scale or similar assessment tools. This approach would better align with the overall clinical effectiveness of therapeutic measures. Additionally measures of effectiveness should be standardized to enable better cross comparison and statistical analysis.

The effectiveness of several interventions covered, particularly Prism adaptation and neuromodulation, appear to be heavily reliant on the neuroanatomical profile of patients. To further explore these neuroanatomical changes, have on treatment reliability and effectiveness future research should stratify participants by lesion location, lesion size and status of interhemispheric pathways. They should also differentiate between different neglect subtypes. Utilizing tools such as fMRI could provide further information helping to identify predictors of responsiveness. These investigations could lead to more individualized treatment depending on patient characteristics.

Combination of different treatment approaches e.g. pairing neuromodulation with conventional therapy or VR assisted rehabilitation could lead to a more effective overall outcome. Future research should include comparison of multimodal interventions compared to single modalities. It should explore potential synergistic effects of combining neuromodulation with task specific training. If data suggests synergistic effects of multimodal therapy, optimal sequencing of modalities should be explored.

To strengthen methodological transparency and improve quality of evidence future studies should preregister trial protocols, explicitly describe randomization and allocation concealment. They should ensure blinded outcome assessment and adhere to CONSORT guidelines for reporting. They should include reporting of adherence, dropout rates and intention to treat analyses. These steps would overall reduce publication bias and create more robust data.

Older patients and chronic phase stroke recovery patients are underrepresented in most trials, despite them constituting a large proportion of clinical population. Future studies should include participants across the full age spectrum, especially focusing on patients in later decades of life. Patients with chronic neglect with strokes occurring more than 6 months ago should be included as well. Viability of technology such as VR applicability for less technologically savvy people should be further assessed. The effect of overall cognitive decline related to age or other comorbidities should be evaluated especially when it comes to more complicated tasks used for rehabilitation. Exploring this field would enable overall better clinical applicability of rehabilitation tools due to the main target of intervention being older patients with a significant amount of them having comorbidities.

While many studies report on whether or not improvements are occurring, very little research regarding the mechanism of change was included. Future studies should investigate cortical activity and network connections via fMRI or EEG, they could also use diffusion imaging to assess changes in white matter integrity. Additional research into biomarkers predicting treatment responsiveness and long-term efficacy could be conducted. A deeper understanding of the neuroplastic mechanisms enabling treatment could lead to a more effective approach and could guide personalized treatment.

5 CONCLUSION AND PRACTICAL RECOMMENDATIONS

When looking at the effectiveness of cognitive rehabilitation with a focus on USN and comparing the findings across the multitude of studies, non invasive brain stimulation particularly TMS seems to be the most effective form of USN rehabilitation currently available. It has the strongest and most consistent evidence out of all the methods examined and shows the most beneficial effect on visual and functional outcomes, especially considering long term usefulness. tDCS also looks promising but lacks research. PA lacks compelling evidence for routine clinical usage despite decades of research due to its inconsistent short-term result and lacking long term benefits. VR and Robot assisted therapy might be useful in a world in which personalized medicine becomes more and more prevalent however current data only shows preliminary results. The limited data suggests that VR therapy might be more useful due to its greater improvement in ADL compared to robot assisted therapy. Mirror therapy while showing beneficial effect on motor recovery, shows no benefit in USN rehabilitation. Thus, TMS and VR appear the most promising for future clinical usage.

Future research should be more methodologically rigorous, should include larger patient populations and should be more focused on improvement of ADLs. The standardization of intervention protocols, assessing long-term effectiveness, integration of neuroimaging and patient stratification are necessary steps to create individualized and more effective treatment approaches. Exploration of multimodal treatment approaches could help guide evidence based clinical practice.

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