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REVIEW ARTICLE (META-ANALYSIS)

Effects of Virtual Reality Intervention on Neural Plasticity in Stroke Rehabilitation: A Systematic Review

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Abstract

Objective: To systematically review and examine the current literature regarding the effects of virtual reality (VR)−based rehabilitation on neural plasticity changes in survivors of stroke.

Data Sources: We searched 6 bioscience and engineering databases, including Medline via EBSCO, Embase, PsycINFO, IEEE Explore, Cumulative Index of Nursing and Allied Health, and Scopus.

Study Selection: We selected studies reporting on the pre-post assessment of a VR intervention with neural plasticity measures published between 2000 and 2021.

Data Extraction: Two independent reviewers conducted study selection, data extraction, and quality assessment. They assessed methodological quality of controlled trials using the Physiotherapy Evidence Database scale and evaluated risk of bias of pre-post intervention and case studies using the National Institutes of Health Quality Assessment Tool.

Data Synthesis: We included 27 studies (n=232). We rated 7 randomized-controlled trials as good quality and 2 clinical-controlled trials as moderate. Based on the risk of bias assessment, we graded 1 pre-post study and 1 case study as good quality, 1 pre-post study and 1 case study as poor, and the other 14 studies as fair. After the VR intervention, main neurophysiological findings across studies include: (1) improved interhemispheric balance; (2) enhanced cortical connectivity; (3) increased cortical mapping of the affected limb muscles; (4) the improved neural plasticity measures were correlated to the enhanced behavior outcomes; (5) increased activation of regions in frontal cortex; and (6) the mirror neuron system may be involved.

Conclusions: VR-induced changes in neural plasticity for survivors of stroke. Positive correlations between the neural plasticity changes and functional recovery elucidates the mechanisms of VR-based therapeutic effects in stroke rehabilitation. This review prompts systematic understanding of the neurophysiological mechanisms of VR-based stroke rehabilitation and summarizes the emerging evidence for ongoing innovation of VR systems and application in stroke rehabilitation.

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Stroke is one of the leading causes of disability in the world, and the long-lasting residual impairments and dysfunctions influence the daily activity and quality of life of a substantial number of survivors of stroke.[1] Physical and occupational therapy, physiatry, speech language pathology, neuropsychology, and nursing have been involved in an interdisciplinary approach for poststroke rehabilitation in a variety of settings to facilitate functional recovery and help patients return to work and life. Rehabilitation interventions also evolve with advancements in theory and evidence from bench to bedside.

Using novel technology in neurorehabilitation has brought promise to advance stroke rehabilitation. As a computer-generated simulation technology, virtual reality (VR) could create an enriched environment, facilitate task-specific training, and provide multimodal feedback to augment functional recovery.[2] The 3 key concepts of VR are immersion, imagination, and interaction.[3] Patients can immerse in and interact with the virtual environment by engaging imagery. VR technology can create games and novel

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tasks not available in the real world, thereby increasing the engagement of patients and eliciting their active participation.[4] In parallel with usual rehabilitation therapy programs, VR can motivate patients to perform more meaningful practices[5] as well as enhance the intensity of purposeful movements.[6] Clinicians have increasingly adopted VR-based rehabilitation, and the emerging research has gradually demonstrated its effects. As a surrogate intervention, VR-based rehabilitation has shown promising results in upper limb function,[7] gait,[8] balance,[9] cognition,[10] and quality of life[11] in survivors of stroke. Recent evidence also presented the benefits of applying VR in the hospital setting for survivors of stroke, including improving functional outcomes and mood states,[12] as well as lowering medical expenditures.[13] Furthermore, the rapidly developing commercially available VR systems, which are relatively inexpensive, portable, and easy-to-use, can be used as home-based programs for patients after discharge to continue rehabilitation.

Functional recovery after brain damage is heavily driven by neural plasticity, which is the adaptive capacity of the central nervous system to undergo structural and functional change in response to experience.[14] Neural plasticity reflects the dynamic change capability of our nervous system across the lifespan. At synaptic level, it presents the changes in the strength of synaptic connections in response to a stimulus or an alteration in synaptic activity in a network.[15] It also involves the axonal remodeling of the cortical pathways and the rearrangements of cortical mapping occurring with disease or recovery.[16] Current understanding of neural plasticity carries implications in rehabilitation, and those implications have been used in practice. To promote experience-dependent neural plasticity and functional recovery, intensive, repetitive, and salient task-specific practices should be used.[17] In addition to taking advantage of the above principles in a simulated media, VR as well as augmented feedback could also enrich training environments by engaging sensory-, cognitive- and perceptive-motor pathways. Therefore, compared with conventional rehabilitation interventions, VR is in a better position to provide the above critical components of neural plasticity to bolster functional recovery outcomes.

Although many reviews in VR and stroke conclude a positive outcome in stroke rehabilitation, most reviews and current studies[2,18,19] focus on the influence of VR-based rehabilitation on impairment and functional measures, but only a few studies[20,21] pay attention to the change occurring in the central nervous system. The underlying neuro-mechanism that drives such clinical impacts in stroke using VR still needs further investigation. The measure and appreciation of neural plasticity could harness the application of VR in rehabilitation. Understanding the effects of VR-based rehabilitation on neural plasticity is critical to elucidate the mechanisms underlying this novel approach and help to identify the neural substrates of recovery to develop effective strategies in VR design and development. Therefore, this systematic review examined the current literature regarding the effects of VR-based rehabilitation on neural plasticity changes with functional recovery in survivors of stroke.

List of abbreviations:

CCT	**controlled clinical trial**
EEG	**electroencephalography**
fMRI	**functional magnetic resonance imaging**
M1	**primary motor cortex**
NIH	**National Institutes of Health**
PFC	**prefrontal cortex**
PMC	**premotor cortex**
RCT	**randomized controlled trial**
S1	**primary somatosensory cortex**
SM1	**primary sensorimotor cortex**
SMA	**supplementary motor area**
TMS	**transcranial magnetic stimulation**
VR	**virtual reality**

Methods

We conducted this systematic review by following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guideline to guarantee high-quality reporting.[22] We registered this review with the International prospective register of systematic reviews (PROSPERO): CRD42020196405.

Literature search

We searched 6 bioscience and engineering databases, including Medline via EBSCO, Embase, PsycINFO, IEEE Explore, Cumulative Index of Nursing and Allied Health, and Scopus for articles. We limited the results to articles published between 2000 and 2021 and in English because the application of VR in rehabilitation began to emerge after 2000. The search strategy, designed by an experienced academic medical librarian (K.H.), combined controlled vocabulary terms and free-text words in the title or abstract on the concepts of virtual reality, stroke, and neural plasticity in applying the inclusion criteria. We finished the final search by May 6, 2021. To minimize bias, we applied a broad search strategy that focused on all patients with a history of stroke. We have included the complete search strategies in the supplemental material (available online only at http://www.archives-pmr.org/).

Eligibility criteria

Articles selected for inclusion in this review meet the following criteria: (1) participants were adult patients aged 18 years and older with the diagnosis of stroke; (2) VR-based rehabilitation was used for intervention; (3) outcomes included neural plasticity, as measured by objective neuroimaging and electrophysiological techniques; (4) the study type was a clinical trial; and (5) the articles were peer-reviewed or conference proceedings. Articles would be excluded if (1) participants had other neurologic diseases; (2) noninvasive brain stimulation or brain-computer interface paradigms were used in combination with VR; and (3) outcomes were only measured at 1 timepoint.

Data extraction

Two reviewers (J.H., H.X.) independently screened the titles and abstracts, then checked the full texts as needed to examine if the articles met the eligible criteria; they excluded irrelevant articles. The details collected from each article included participant characteristics, study type, interventions, control groups, VR type and setting, neural plasticity measurement tools, and outcome results. Any disagreement during this process was settled by group discussion, and the final decision will be made with the third experienced reviewer (K.C.S.). Interrater reliability was assessed using percentage agreement and Cohen κ coefficient after screening.

Interrater agreement of eligibility by abstract was very good (κ=84.1%; 95% confidence interval, 0.65-1.03).

Quality assessment

We used the Physiotherapy Evidence Database scale to evaluate the methodological quality of all the included randomized controlled trial (RCT) and controlled clinical trial (CCT). This scale was developed to identify trials that are likely to be internally valid and have sufficient statistical information to guide clinical decision making.[23] There are 11 items in this scale, with the last 10 items counting 1 point each, and the total score range is 0-10. Higher scores indicate better study quality. The common interpretation of the total score of an article was 6-10 as good quality, 4-5 as moderate quality, and 0-3 as low quality.[24] The reviewers evaluated the risk of bias assessment for other study designs by the National Institutes of Health (NIH) Quality Assessment Tool. They evaluated single-arm trials using the NIH Quality Assessment Tool for before- and after-studies with no control group,[25] and evaluated case studies by the NIH Quality Assessment Tool for case series studies [26] The reviewers independently scored the included studies and identified discrepancies and solved them with a third experienced reviewer. The quality assessment tool provides a rating for low, fair, or high risk of bias. Interrater agreement of risk of bias assessment was fair (κ= 27.4%; 95% confidence interval, −0.11 to 0.66).

Data synthesis

We conducted a narrative synthesis of the data from the identified studies, including participants characteristics, study type, interventions, control group, VR intervention, neural plasticity measures, and functional outcome results.

Results

Studies identification

We identified 232 records from 6 databases and another 4 records through our reference list. After removing duplicates, 142 records remained and were screened. We assessed 29 full-text articles for eligibility and included 27 studies in this systematic review. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis flowchart in figure 1 demonstrates the process of study identification and the reasons for excluding the 3 studies. Among the included studies, 6 were RCTs, 2 were CCTs, 11 were pre-post single-arm trials, and 7 were case series/studies. Table 1 summarizes the characteristics of these studies.

VR systems for intervention

Twenty-four studies focused on sensorimotor rehabilitation, and there was a fair amount of variation regarding VR systems. Among them, 3 studies focused on lower extremity function,[27-29] 1 on balance training,[30] and the remaining 20 on upper extremity function.[21,31-49] Two studies[27,28] use VR-enhanced treadmills for locomotion training, and 1 used IREX lower extremity games.[29] Nintendo Wii Fit games were used for balance training.[30] Seven of the 19 studies used the NJIT-RAVR system for upper extremity, which combined VR with robotic training.[35,36,38,41,43,47,49] Other studies used Leap motion-based VR,[42] IREX VR upper extremity games,[21,33] Kinect-based VR,[31] robotic VR system,[37,40] Rehabilitation Gaming System,[34] VR-based bilateral upper-extremity training,[32] immersive VR mirror therapy,[45] customized immersive VR,[44] EMG-based VR neurofeedback system,[46] and an early prototype of VR rehabilitation system.[39]

For cognition rehabilitation, 2 single-arm studies used VR in chronic survivors of stroke with unilateral visuospatial neglect.[50,51] The same 3-dimensional VR apparatus was used in both studies for visual scanning training. Another single case study used the BTS NIRVANA system for the treatment of neglect.[52]

To facilitate the depiction of different VR systems' features and special advantages, we extracted the therapeutic advantages from each study by adopting and modifying the approach by Maier et al.[53] Those therapeutic advantages reflected the neurorehabilitation principles that have shown effectiveness in motor recovery by driving neural plasticity. Table 2 summarizes these principles. For design, we assigned the VR intervention of each study to 1 of 3 categories based on the immersion level: nonimmersive, semi-immersive, and fully immersive.[54] Definitions and examples of these 3 categories are also summarized in Table 2.

Quality assessment

With Physiotherapy Evidence Database scoring, all 6 included RCTs scored above 6, which was considered as good quality; the 2 CCTs both scored 5, which was considered as moderate quality. As shown in table 3, all 8 studies scored points on item 4 (groups were similar at baseline) and items 8-11. However, they rarely scored points on item 5 (blinding of participants) and item 6 (blinding of therapists), which is understandable owing to the nature of intervention studies. Table 4 summarizes the NIH quality assessment results of pre-post and case studies. Most studies were evaluated as fair quality; 2 studies had good quality and 2 had poor quality.

Neural plasticity measurements

To conclusively measure neural plasticity, we used 4 noninvasive neuroimaging and electrophysiological techniques, including functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and transcranial magnetic stimulation (TMS). Table 5 has a detailed summary for each study and a simplified checklist.

Functional magnetic resonance imaging

A series of studies reported increased activation of ipsilesional primary sensorimotor cortex (SM1) after VR intervention . Interhemispheric dominance was calculated by the lateral index; although the formula and interpretation were varied across studies, most of them consistently showed the shift of activation from the contralesional to the ipsilateral hemisphere. [27,29,31,36,38,41,42,48] You et al[29] found the lateral index value after VR intervention was comparable to healthy participants. However,1 study showed the opposite phenomenon, which was the contralesional activation of the primary motor cortex (M1).[21] For the supplementary motor area (SMA), another study found increased bilateral activation,[27] whereas yet another showed decreased widespread bilateral activation along with the contralesional premotor cortex (PMC)[33]; studies also noted increased ipsilesional activation[39] and decreased contralesional activation.[35] For the cerebellum, 1 study

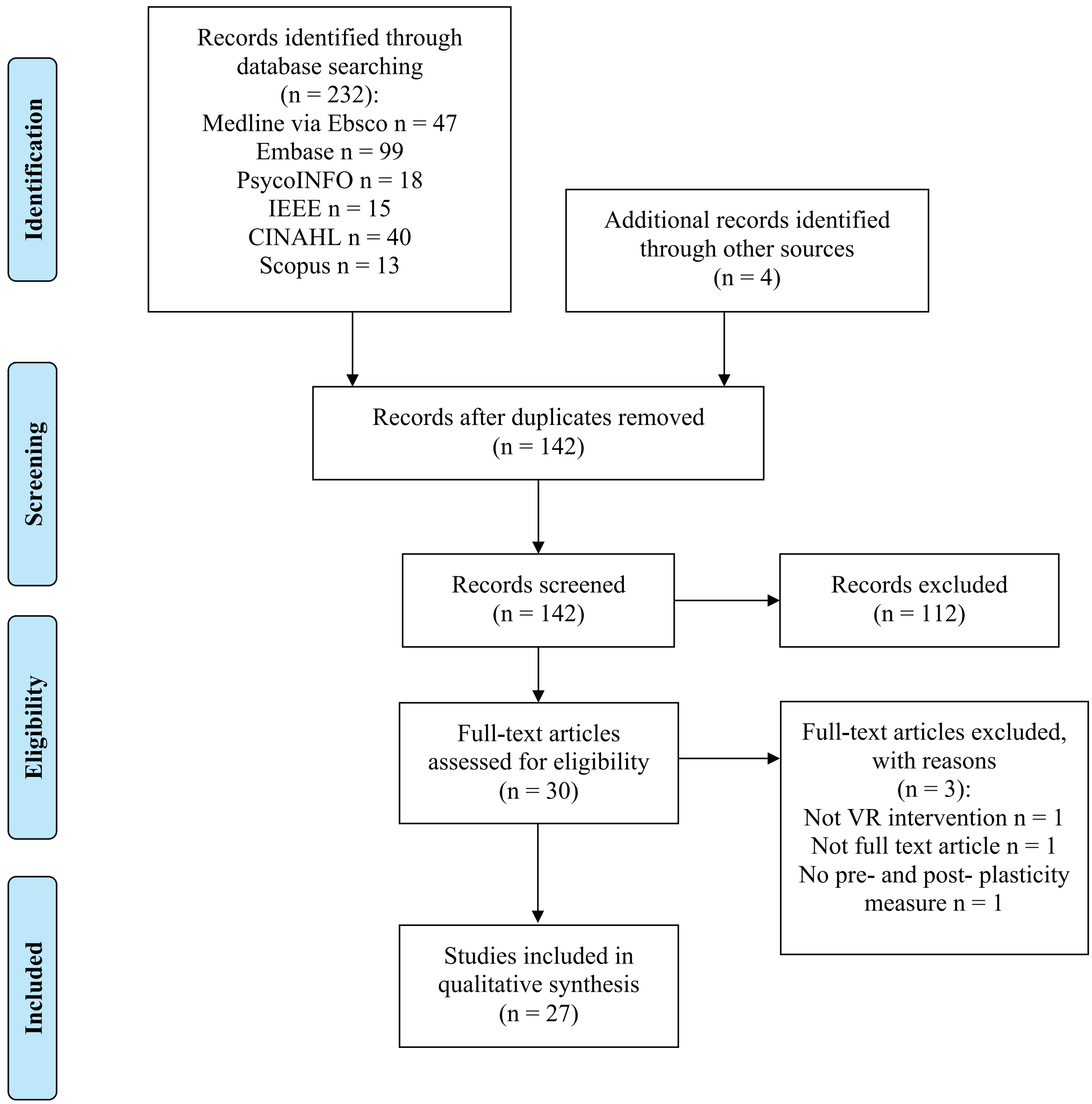

Fig 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analysis flowchart.

showed increased recruitment[21]; 2 cases studies showed an increase[31] and a decrease[40] of cerebellum activation, respectively. Prominent prefrontal cortex (PFC) activation was noted after VR intervention.[21]

Connectivity was a measure of correlation among different brain function regions. Compared with brain activation as a functional segregation concept, connectivity was more focused on the functional integration.[55] Increased functional connectivity was shown between bilateral SM1,[38] contralesional M1,[35,45] and ipsilesional M1; and between bilateral primary somatosensory cortex (S1), ipsilesional superior parietal gyrus, cerebellum and ipsilesional M1.[45] Task-related connectivity also showed an increase between ipsilesional M1 and SMA.[35] In another study,[36] functional connectivity between the ipsilesional M1 and other regions of the brain did not have significant differences between the VR group and control groups; instead, the change of effective connectivity was found in the VR group, which was the facilitation of ipsilesional M1 by S1. Functional connectivity within the dorsal attention network was also found to increase after VR training for spatial neglect.[51] VR intervention increased the task-evoked brain activity in an extended network during attentional cuing, which included the PFC and temporal cortex.[50]

Electroencephalography

Two RCTs found the VR group to elicit higher cortical activation within the frontoparietal region. One study[32] found that, compared with conventional bilateral upper extremity training, the VR-based bilateral upper extremity training induced higher concentration of brain activity in both hemispheres. The other study[28] also found more evident activation of the premotor, precuneus, and associative visual areas in the VR-based Lokomat training, in which areas that the mirror neuron system might be encompassed. Event-

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Table 1 Study characteristics

Study	Study Design	Imaging	Sample Size	Lesion	Stage	Intervention	Dosage	VR Type	Behavior Outcomes
Jang et al[33]	Randomized controlled trial	fMRI	10 (VR 5, control 5)	Subcortical	Chronic >6 months	IREX VR games for UE Passive control: no intervention	60 min × 5 d × 4 w	Nonimmersive	FMA, BBT, MFT
You et al[29]	Randomized controlled trial	fMRI	10 (VR 5, control 5)	Cortical and subcortical	Chronic >1 year	IREX VR games for LE Passive control: no intervention	60 min × 5 d × 4 w	Nonimmersive	FAC, MMAS
Lee et al[32]	Randomized controlled trial	EEG	18 (VR 10, control 8)	Not mentioned	Chronic >6 months	VR UE training Active control: UE training	30 min × 3 d × 6 w	Nonimmersive	None
Ballester et al[34]	Randomized controlled trial	TMS	35 (VR 17, control 18)	Not mentioned	Chronic >1 year	Rehab Gaming System for UE Active control: conventional therapy	20 min × 1-3 sessions × 5 d × 3 w	Semi-immersive	FMA, CAHAI
Calabrò et al[28]	Randomized controlled trial	EEG	24 (VR 12, control 12)	Cortical	Chronic >6 months	Lokomat treadmill with VR Active control: Lokomat	40 min × 5 d × 8 w	Semi-immersive	RMI, POMA
Wang et al[42]	Randomized controlled trial	fMRI	26 (VR 13, control 13)	MCA stroke	Subacute 8 weeks	Leap motion VR + PT Active control: OT + PT	45 min × 5 d × 4 w	Nonimmersive	WMFT
Mekbib et al[44]	Randomized controlled trial	rs-fMRI	23 (VR 12, control 11)	Not mentioned	Subacute 3 months	MNVR-Rehab for UE + OT Active control: time-matched OT	1 h × 4 d × 2 w	Immersive	FMA, BI
Saleh et al[36]	Controlled clinical trial	fMRI	19 (VR 10, control 9)	Cortical and subcortical	Chronic >1 year	Robot-assisted VR (NJIT-RAVR) for UE Active control: repetitive task practice	3 h × 4 d × 3 w	Semi-immersive	JTHFT
Patel et al[43]	Controlled clinical trial	TMS	13 (VR 7, control 6)	Cortical and subcortical	Acute and early subacute 1 months	Robot-assisted VR (NJIT-RAVR) for UE + conventional therapy Passive control: conventional therapy	1 h × 8 sessions	Semi-immersive	FMA, WMFT
Bao et al[31]	Pre-post single group	fMRI	5	Cortical and subcortical	Subacute 3 months	Kinect-based VR for UE	60 min × 5 d × 3 w	Non immersive	FMA, WMFT
Ekman et al[50]	Pre-post single group	fMRI	12	Cortical and subcortical	Chronic >1 year	RehAtt VR 3D game for neglect training	60 min × 3 d × 5 w	Semi-immersive	Posner cuing task in fMRI
Orihuela-Espina et al[21]	Pre-post single group	fMRI	8	Subcortical	Chronic >6 months	IREX VR gaming system gesture therapy	45 min × 20 sessions	Semi-immersive	FMA, Motricity index
Mekbib et al[45]	Pre-post single group	rs-fMRI	12	Cortical and subcortical	Subacute 3 months	Immersive VR mirror therapy + conventional therapy	60 min × 4 d × 2 w	Full-immersive	FMA
Omiyale et al[30]	Pre-post single group	TMS	10	Not mentioned	Chronic >1 year	Nintendo Wii Fit balance	60 min × 3 d × 3 w	Nonimmersive	Balance: reaction time, TUG
Marin-Pardo et al[46]	Pre-post single group	EEG	4	Not mentioned	Chronic >1 year	EMG based VR feedback for wrist extension activation	1 h × 7 sessions	Full-immersive	FMA, ARAT, Wrist ROM, SIS-16
Patel et al[47]	Pre-post single group	TMS	5	Cortical and subcortical	Acute and subacute 47 days	Robot-assisted VR (NJIT-RAVR) for UE + conventional therapy	60 min × 5 d × 2 w	Semi-immersive	FMA, WMFT
Turolla et al[48]	Pre-post single group	fMRI	15 (Only 1 received fMRI)	MCA ischemic stroke	Chronic >6 months	Haptic robotics VR	45 min × 5 d × 3 w	Semi-immersive	FMA, NHPT, Kinematics data
Wåhlin et al[51]	Pre-post single group	rs-fMRI	13	Not mentioned	Chronic >6 months	RehAtt VR 3D game for neglect training	60 min × 3 d × 5 w	Semi-immersive	None
Xiao et al[27]	Pre-post single group	fMRI	8	Cortical and subcortical	Subacute 42 days	VR enhanced treadmill	5 sessions × 3 w	Nonimmersive	FMA, Brunel, 10 m walk time, Gait speed
Yarossi et al[49]	Pre-post single group	TMS	17	Cortical and subcortical	Subacute 3 months	Robot-assisted VR (NJIT-RAVR) for UE + conventional therapy	8 sessions	Semi-immersive	FMA, WMFT, BBT, Kinematic and kinetic measures
Schuster-Amft et al[39]	Case series	fMRI	2	Subcortical	Chronic >1 year	VR rehab system for UE	45-60 min/d × 4 w	Semi-immersive	CAHAI, VR performance
Comani et al[37]	Case series	EEG	3	Cortical and subcortical	Subacute 3 weeks	Robotics VR system	3 sessions × 4 w	Semi-immersive	Kinematics measures

(*continued on next page*)

Table 1 (*Continued*)

Study	Study Design	Imaging	Sample Size	Lesion	Stage	Intervention	Dosage	VR Type	Behavior Outcomes
Saleh et al[38]	Case series	fMRI	4	Cortical and subcortical	Chronic >1 year	Robot-assisted VR (NJIT-RAVR) for UE	3 h × 8 d	Semi-immersive	WMFT, JHFT, Kinematics measure
Saleh et al[35]	Case series	rs- and task- fMRI	2	Cortical and subcortical	Chronic >6 months	Robot-assisted VR (NJIT-RAVR) for UE	3 h × 4 d × 2 w	Semi-immersive	FMA, WMFT
Comani et al[40]	Single case	EEG	1	Cortical	Subacute 3 weeks	Robotics VR system	3 sessions × 4 w	Semi-immersive	NHPT, Motricity index, Kinematics measure
De Luca et al[52]	Single case	EEG	1	Not mentioned	Not mentioned	BTS NIRVANA VR system for neglect training	40 sessions	Semi-immersive	Psychometric battery
Tunik et al[41]	Single case	fMRI	1	Subcortical	Chronic >1 year	Robot-assisted VR (NJIT-RAVR) for UE	5 sessions × 2 w	Semi-immersive	None

Abbreviations: 3D, 3-dimensional; ARAT, Action Research Arm Test; BBT, Box and Block Test; BI, Barthel Index; CAHAI, Chedoke Arm and Hand Activity Inventory; FAC, Functional Ambulation Category; FMA, Fugl-Meyer Assessment; JTHFT, Jebsen-Taylor Hand Function Test; MCA, middle cerebral artery; MFT, Manual Function Test; MMAS, Modified Motor Assessment scale; NHPT, Nine Hole Peg Test; NJIT-RAVR, New Jersey Institute of Technology Robot-Assisted Virtual Rehabilitation; OT, occupational therapy; POMA, Performance Oriented Mobility Assessment; PT, physical therapy; RMI, Rivermead Mobility Index; rs-fMR, resting state fMRI; SIS-16, sixteen-question stroke impact scale; UE, upper extremity; WMFT, Wolf Motor Function Test.

related spectral perturbations were lateralized in the affected hemisphere.

The same research group conducted another 2 cases studies, with 3 participants and 1 participant, respectively.[37,40] The high resolution-EEG system was used synchronously with the VR training system to measure cortical activity during tasks. The 3 cases showed mixed results for the interhemispheric dominance measured by lateral index of SM1 and the activation of inferior frontal gyrus observed during the VR tasks.[37] One case presented reduced bilateral over-recruitment of SM1 and the cerebellum, especially in the ipsilesional hemisphere, and improvement of the oscillatory processing pattern, which tended to return to normal.[40] A single case study reported increased event related potential P300 amplitude of the ipsilesional hemisphere, which was correlated with the improvement of cognitive function scores and standard neglect test.[52] Another study with 4 participants found enhanced corticomuscular coherence at beta band.[46]

Transcranial magnetic stimulation

In a CCT, a significant expansion of ipsilateral M1 TMS mapping of hand muscles was shown during the intervention period, whereas there was no significant difference between the VR and control groups.[43] In another study, the corticospinal excitation of the tibialis anterior muscle was improved in interhemispheric symmetry after the VR balance training.[30] Two studies found an increased TMS mapping of the affected first dorsal interosseous side.[47,49] In an RCT, only the VR group used the navigated TMS to assess corticospinal excitability and cortical reorganization. The results revealed enhanced excitability of the distal muscle in the affected side as well as a displacement of centroid of cortical map in the lesioned hemisphere.[34]

Functional outcome measure

In addition to neural plasticity outcomes, many studies also collected functional outcome data. These measures ocused on the body structure/function impairments and activity limitation domains of the ICF model. The detailed information is listed in table 1, and the correlation between functional outcome measures and neural plasticity measures is in table 5.

Discussion

Although VR has been increasingly used in stroke rehabilitation and various clinical trials and systematic reviews have demonstrated its clinical effects, the underlying neurophysiological mechanisms are not fully understood. This systematic review aimed to evaluate and summarize the current evidence of VR-induced neural plasticity in survivors of stroke. After a period of VR intervention, the common neurophysiological findings include: (1) improved interhemispheric balance, with a shift of activation from the contralesional to the ipsilesional SM1 dominance during the paretic limb movement[27,29,31,33,35,36,38,39,41,42,48]; (2) enhanced connectivity between different functional areas[35,36,38,45,51]; (3) increased cortical representation mapping of the affected limb muscles[43,47,49]; (4) improved neural plasticity measures were correlated to enhanced behavior outcomes[21,27,34,36,45,49,52]; (5) increased activation of regions in the frontal cortex[21,28,32,50]; and (6) the mirror neuron system may be involved in VR interventions[28,37].

Table 2 Therapeutic advantages of the VR systems used in the studies

VR System	Therapeutic Advantages
Nonimmersive VR: The desktop or laptop screens are typically used to present the virtual environment to the user, and the user experiences low sense of immersion and interaction in the virtual environment. The platform does not fully occlude the user's field of view. Examples: computer monitor, TV screen.	
Kinect-based VR[31]	Promote the use of the impaired limb
VR bilateral UE training[32]	Structured practice Augmented feedback
Nintendo Wii Fit[30]	Variable practice
Leap motion VR[42]	Task-oriented practice Avatar representation Promote the use of the impaired hand
VR enhanced treadmill[27]	Task-oriented practice Progressive difficulty levels
Semi-immersive VR: A partially virtual environment is provided for the user to interact with. The user's sense of immersion and interaction is between the nonimmersive and full immersive VR. Examples: panoramic TV, large screen projector system.	
An early prototype of a VR system[39]	Task-oriented practice Progressive difficulty levels Avatar representation Mirror feedback
Rehab Gaming System[34]	Task-oriented practice Variable practice Progressive difficulty levels Avatar representation Multisensory stimulation Augmented feedback
IREX VR games[29,33]	Task-oriented practice Progressive difficulty levels Variable practice Avatar representation Implicit feedback: knowledge of performance Explicit feedback: knowledge of results Faded feedback
IREX VR games gesture therapy[21]	Task-oriented practice Progressive difficulty levels Variable practice Promote the use of the impaired limb
Lokomat with VR[28]	Task-oriented practice Tailored robot haptic assistance Multisensory feedback Avatar representation
Robotics VR system[37,40]	Task-oriented practice Progressive difficulty levels
Haptic robotics VR[48]	Task-oriented practice Progressive difficulty levels Tailored robot haptic assistance
NJIT-RAVR[35,36,38,41,43,47,49]	Task-oriented practice Progressive difficulty levels Tailored robot haptic assistance Avatar representation
RehAtt VR 3D game for neglect[50,51]	Multisensory stimulation Progressive difficulty levels Variable practice
BTS BIRVANA VR system for neglect[52]	Multisensory stimulation Progressive difficulty levels Avatar representation
Full immersive VR: Immersive VR encompass the overall sense of the user. The real world is totally displaced by the virtual environment. The sense of immersion and interaction are the highest. The platform fully occludes the users' field of view. Examples: head mounted display, CAVE.	
Immersive VR mirror therapy[45]	Task-oriented practice Progressive difficulty levels Mirror therapy
EMG based VR feedback system[46]	Task-oriented practice Progressive difficulty levels EMG biofeedback Avatar representation
MNVR-Rehab system[44]	Task-oriented practice Progressive difficulty levels Mirror therapy

Table 3 Physiotherapy Evidence Database assessment scores for randomized controlled and clinical controlled trials

	Eligibility Criteria	Random Allocation	Concealed Allocation	Baseline Comparability	Blind Participants	Blind Therapists	Blind Assessors	Adequate Follow-Up	Intention-to-Treat	Between Group Comparisons	Point Estimates and Variability	Total Score
Ballester et al[34]	Yes	1	0	1	0	0	0	1	1	1	1	6
Calabrò et al[28]	Yes	1	1	1	1	0	1	1	1	1	1	9
Jang et al[33]	Yes	1	1	1	0	0	0	1	1	1	1	7
Lee et al[32]	Yes	1	0	1	0	0	0	1	1	1	1	6
Mekbib et al[44]	Yes	1	1	1	0	0	1	0	1	1	1	7
Saleh et al[36*]	Yes	0	0	1	0	0	0	1	1	1	1	5
Patel et al[43*]	Yes	0	0	1	0	0	0	1	1	1	1	5
Wang et al[42]	Yes	1	0	1	0	0	1	1	1	1	1	7
You et al[29]	Yes	1	0	1	0	1	1	1	1	1	1	8

* Indicates a clinical controlled trial.

VR intervention

A mix of VR paradigms were found across the included studies, and there were some studies using the same VR systems (see table 5). VR is not a universal intervention, although some basic concepts and features are shared across different VR systems. Each VR system could be different from others regarding virtual environment platforms, task complexity, user experience, and other factors, depending on the purpose and technology used in product design. However, most systematic review and meta-analysis studies tends to combine those different VR systems and explore the overall effectiveness. Although the diverse VR systems included in this systematic review harness the inclusiveness, it could also lead to difficulty in the interpretation of the results. This is especially true for the neutral results, which are commonly seen in rehabilitation studies.

In this review, most studies used specific VR systems and only 2 used the off-the-shelf VR gaming systems (Kinect and Nintendo). The specific VR systems were designed for the purpose of rehabilitation and involved tangible user interfaces and focused the skills transfer to functional activities.[10] Some of them were still at the early exploratory phase and strictly used in research. In contrast, commercial VR games were play based and recreation purposed and could be more portable, accessible, and inexpensive to use. With the ongoing debates on whether one type is superior to the other in stroke rehabilitation,[2,56] a recent meta-analysis demonstrated that the specific VR systems were more effective than commercial VR games in upper limb recovery.[53] Owing to only 2 included articles reporting on commercial VR systems, comparison of these 2 types of VR systems in this review was not feasible, and the results should be interpretated with caution.

Immersion level is an important feature of VR because it reflects the design of virtual environment and directly influences the user's sense of presence and enjoyment.[57] Presence could indicate the extent to which the virtual environment represents the real world for the user.[54] Although immersion has been discussed in other fields regarding VR design, little attention has been paid to explore its implication in rehabilitation. Based on the limited number of studies, there is a mixed result of the effect of different levels of VR immersion on performance outcomes. Compared with regular computer monitors, participants in the immersive CAVE system reported more presence and better learning experience.[58] A positive relationship was found between immersion and retrieval movements for virtual objects in survivors of stroke.[59] There was no significant difference in upper extremity motion when the VR was displayed via fully immersive compared with semi-immersive devices.[60] An RCT found that the nonimmersive VR Nintendo Wii system was not superior to recreational activity for upper extremity function recovery in survivors of stroke.[61] One study reported the effect of immersion level on cortical activity. Slobounov et al[62] found that fully immersive VR required more brain and sensory resource allocation in motor tasks than less immersive VR, which indicated that specific VR design could elicit specific brain recruitment pattern during tasks. Among the 26 studies included this systematic review, 6 used nonimmersive VR, 18 used semi-immersive VR, and 2 used fully immersive VR. We found that each immersion level of VR could induce neural plasticity changes, although the outcome could not be directly compared among the 3 categories of immersion owing to the heterogeneity of the tools to measure neural plasticity. Whether immersion level could affect neural plasticity in VR intervention studies remains unknown. It is important to take VR features into consideration for the future studies that focus on the effects of VR in rehabilitation.

Table 4 NIH quality assessment results for pre-post and case studies

Study	Type	Good	Fair	Poor
Schuster-Amft et al[39]	Case series	√		
Bao et al[31]	Pre-post		√	
Comani et al[37]	Case series			√
Comani et al[40]	Case series		√	
Ekman et al[50]	Pre-post		√	
Orihuela-Espina et al[21]	Pre-post		√	
De Luca et al[52]	Case series		√	
Mekbib et al[45]	Pre-post		√	
Omiyale et al[30]	Pre-post		√	
Marin-Pardo et al[46]	Pre-post		√	
Patel et al[47]	Pre-post			√
Saleh 2011[38]	Case series		√	
Saleh 2012[35]	Case series		√	
Tunik et al[41]	Case series		√	
Turolla et al[48]	Pre-post		√	
Wåhlin et al[51]	Pre-post		√	
Xiao et al[27]	Pre-post		√	
Yarossi et al[49]	Pre-post	√		

Levin[63] proposed that VR could offer enriched environments for rehabilitation, which provided a putative explanation of why VR could affect neural plasticity. The enriched environment refers to the housing conditions that facilitate the enhanced motor, sensory, cognition stimulation, and social interaction compared with the standard housing conditions.[64] The enriched environment could promote the experience-dependent plasticity in stroke, with the effects shown at the molecular,[65] cellular,[66,67] and behavioral[68,69] levels. Compared with conventional rehabilitation approaches, VR illustrates the main components of environmental enrichment by creating an immersive and interactive environment with multimodal stimulation to engage the active participation of the patients. With the 2 main components, enriched environment and environmental novelty and complexity, a more intensive learning experience could be achieved.[63] VR has a promising potential to transfer the core tenets of enriched environment from animal models to clinical rehabilitation and offer individualized training environments to drive neural plasticity and optimize functional recovery.

Neural plasticity measurements

In the preclinical studies, neural plasticity could be measured at the molecular, synaptic and cellular levels on the animal models, whereas the 2 commonly used methods for the human participants are neuroimaging and electrophysiological techniques. More than half of the included studies used fMRI to measure neuroimaging outcomes. Using the blood oxygen level dependent signal as an indirect measure of neural activity, fMRI is able to identify patterns of brain activation during motor task or resting at high spatial resolution, but the temporal resolution is poor. EEG is portable and less expensive than fMRI but has poor spatial resolution and only limits to the cortical activity. As a noninvasive brain stimulation protocol, TMS could be used to both modulate and measure the brain excitability and plasticity, as well as provide cortical mapping for the motor area. The information we can get from these neural plasticity measures could serve as neurophysiological biomarkers to inform prognosis and precise intervention.[70] A systematic review including 13 fMRI studies indicated that identifying certain patterns of cortical activation through fMRI could suggest time-dependent reorganization in cerebral networks that accompany functional recovery post stroke.[71] In patients with a favorable recovery, the overactivations of primary and association motor areas are transient and tend to return to original state, whereas in patients with poor recovery, the altered brain activation is typically persistent.[71] Furthermore, a longitudinal fMRI study showed the improvement of motor function measured by Medical Research Council scale was significantly correlated with the lateral index, one of the main parameters calculated through the results of fMRI (r=0.85. P<.05).[72] Another meta-analysis examined the neural plasticity changes demonstrated by TMS and fMRI after movement-based therapy in survivors of stroke, and found neural changes accompany the mitigation of motor function deficits.[73] Significant correlations between pre-post lateral index changes of motor map area measured by TMS and hand motor function was found, at both the first (r=0.62, P=.04) and second (r=0.61, P=.06) follow-up evaluation.[74] The reliability of fMRI[75] and TMS[76] to evaluate change in individuals with stroke was also substantiated (intraclass correlation coefficient>0.70). By measuring the electrical activity of the brain, EEG can identify salient neural substrates underlying specific functional impairments, aid the selection of intervention, and provide better prognostic information.[77] Quantitative EEG parameters displayed not only clinical relevance but also multilevel reproducibility and reliability in the evaluation of the population with stroke (intraclass correlation coefficient >0.90).[78] Above all, the neural plasticity measure techniques used in the included studies are valid approaches to correlate the objective functional measures that are valid and reproducible. The use of aforementioned techniques can aid rehabilitation professionals to appreciate the individual's spatial and temporal neural plasticity change patterns after VR intervention, thus granting the potential to track recovery progress, establish patient's response, and tailor the training modules to fit the individualized program.

Improved interhemispheric balance

Motion execution of 1 extremity is mainly innervated by the contralateral M1 though the corticospinal tract with some

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Table 5 Effects of VR intervention on neural plasticity: summary and checklist

Study	VR	Neural Plasticity Assessment Types and Outcomes	Improved Interhemispheric Balance	Enhanced Cortical Connectivity	Increased TMS Mapping	Correlation With Functional Outcomes	Increased Frontal Cortex Activation	Mirror Neuron System Involvement
Nonimmersive VR								
Bao et al[31]	Kinect-based VR	fMRI: 4 in 5 cases increased the contralateral activation of SM1; 1 case decreased the extent but increased the magnitude of SMA and CRB activation.	√					
Lee et al[32]	VR bilateral UE training	EEG: Increased concentration and brain activity of the frontal lobe.					√	
Omiyale et al[30]	Nintendo Wii Fit	TMS: Increased interhemispheric symmetry of corticomotor excitability induced by tibialis anterior muscle.	√					
Wang et al[42]	Leap motion VR	fMRI: Shift in SMC activation from ipsilateral to contralateral (LI), increased contralateral SMC activation.	√					
Xiao et al[27]	VR enhanced treadmill	fMRI: Increased ipsilesional SMC and bilateral SMA activation. Correlation: increased SMC was correlated with decreased 10 m walking time.	√			√		
Semi-immersive VR								
Schuster-Amft et al[39]	An early prototype of a VR system	fMRI: Decreased bilateral activation, increased ipsilesional SM1 and SMA activation.	√					
Ballester et al[34]	Rehab Gaming System	TMS: Enhanced excitability of CST for the distal APB muscle, centroid displacements of the cortical map for both APB and ECR. Correlation: centroid displacement of the ECR is positively correlated with the CAHAI improvement.				√		
Calabrò et al[28]	Lokomat with VR	EEG: Stronger event-related spectral perturbations in the high-γ and β bands and larger fronto-central cortical activations in the affected hemisphere. More evident activation of premotor, precuneus and associative visual areas. ERSPs were lateralized in the affected hemisphere. The mirror neuron system may be encompassed.					√	√
Comani et al[40]	Robotics VR system	EEG: 1 case showed reduced bilateral over-recruitment of SM1 and CRB, especially in the ipsilesional hemisphere; improvement of the oscillatory processing pattern						
Comani et al[37]		EEG: 3 cases showed a mixed results of LI shift; activation of IFG during VR rehabilitation process.						√
Orihuela-Espina et al[21]	IREX VR games gesture therapy	fMRI: Contralesional activation of the unaffected M1, CRB recruitment, and compensatory PFC activation were the most prominent strategies evoked. Correlation: positive correlation between motor dexterity and total brain recruited activity.				√	√	

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Table 5 (*Continued*)

Study	VR	Neural Plasticity Assessment Types and Outcomes	Improved Interhemispheric Balance	Enhanced Cortical Connectivity	Increased TMS Mapping	Correlation With Functional Outcomes	Increased Frontal Cortex Activation	Mirror Neuron System Involvement
Jang et al[33]	IREX VR system	fMRI: Increased ipsilesional SM1 activation (LI), decreased widespread bilateral activation of SM1, SMA and contralesional PMC.	√					
You et al[29]		fMRI: Shift in SMC activation from ipsilateral to contralateral (LI), the LI value after VR was comparable to normal subjects.	√					
Turolla et al[48]	Haptic robotics VR	fMRI: 1 case showed decreased ipsilateral activation and the activation of the affected hemisphere was closer to the normal pattern.	√					
Patel et al[47]	NJIT-RAVR	TMS: 2 cases showed increased volume and area of FDI mapping of the paretic hand, improved cortical excitability			√			
Patel et al[43]		TMS: both groups showed increased ipsilesional TMS map area during treatment, no between group difference. However, as an additional intervention, VR showed enhanced impairment and behavior outcomes.			√			
Saleh et al[38]		fMRI: 3 of 4 cases increased ipsilesional M1 (LI), increased functional connectivity between ipsilesional M1 and bilateral SM1.		√				
Saleh et al[35]		rs-&task- fMRI: 2 cases showed decreased extent of activation of contralesional M1 and SMA; 1 case showed decreased functional connectivity between iM1 and cM1, the other showed increased; both 2 cases showed increase in task related connectivity between ipsilesional M1 and SMA.		√				
Saleh et al[36]		fMRI: Reduced magnitude and extent of activation compared with repetitive task practice group, shift in SMC activation form contralesional to ipsilesional (LI); facilitation of M1 by S1 (effective connectivity). Correlation: correlation between ipsilesional M1, ventral premotor area, bilateral S1 and JTHFT changes; effective connectivity and posttest JTHFT.	√	√		√		
Tunik et al[41]		fMRI: 1 case showed increased activation of ipsilesional M1.	√					
Yarossi et al[49]		TMS: Increased TMS map of FDI muscle in ipsilesional hemisphere. Correlation: for the MEP+ patients, increased FDI in ipsilesional hemisphere had significant correlations with improvement of WMFT, BBT and finger AROM; but not for the MEP- patients.			√	√		

(*continued on next page*)

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Table 5 (*Continued*)

Study	VR	Neural Plasticity Assessment Types and Outcomes	Improved Interhemispheric Balance	Enhanced Cortical Connectivity	Increased TMS Mapping	Correlation With Functional Outcomes	Increased Frontal Cortex Activation	Mirror Neuron System Involvement
Ekman et al[50]	RehAtt VR 3D game for neglect	fMRI: Increased activation of the PFC, including the anterior cingulate cortex and dorsolateral PFC; increased activation in the bilateral middle and superior temporal gyrus					√	
Wåhlin et al[51]		rs-fMRI: Longitudinal increase in interhemispheric functional connectivity in the dorsal attention network, between right frontal eye field and left intraparietal sulcus.		√				
De Luca et al[52]	BTS BIRVANA VR system for neglect	EEG: Increased ERP P300 amplitude of the impaired hemisphere (return back to the normal). Correlation: Increased ERP 300 was correlated with improvement in cognitive function scores and time in standard neglect tests.				√		
Full immersive VR								
Mekbib et al[45]	Immersive VR mirror therapy	rs-fMRI: Increased functional connectivity between contralesional M1, bilateral S1, ipsilesional superior parietal gyrus, CRB with lesioned M1. Correlation: the increased M1-M1 connectivity is positively correlated to the change of FMA.		√		√		
Marin-Pardo et al[46]	EMG based VR feedback system	EEG: Enhanced corticomuscular coherence at beta band (12-30 Hz).						
Mekbib et al[44]	MNVR-Rehab system	rs-fMRI: Functional connectivity maps associated with the M1 were reestablished in the contralesional brain regions, including the M1, S1, superior frontal gyrus and superior parietal gyrus.		√				√

Abbreviations: APB, abductor pollicis brevis; AROM, active range of motion; BBT, Box and Block Test; CAHAI, Chedoke Arm and Hand Activity Inventory; CRB, cerebellum; CST, corticospinal tract; ECR, extensor carpi radialis; ERP, event-related potential; ERSP, event-related spectral perturbation; FDI, first dorsal interosseous; FMA, Fugl-Meyer assessment; IFG, inferior frontal gyrus; JTHFT, Jebsen-Taylor Hand Function Test; LI, lateral index; MEP, motor evoked potential; SMC, sensorimotor cortex; UE, upper extremity; WMFT, Wolf Motor Function Test involvement of the ipsilateral hemisphere through transcallosal connections.[79,80] However, brain injury could affect the interhemispheric interaction that participates motor control. In the early stage of stroke, over-recruitment of the contralesional SM1 is commonly induced by paretic limb motion. This abnormal brain activation pattern and interhemispheric imbalance have been interpreted by GABA-A receptor-mediated short-interval intracortical inhibition and GABA-B receptor mediated interhemispheric inhibition.[81] Reduced inhibition signals from the lesioned hemisphere contribute to the overactivation of the intact hemisphere. In turn, the intact hemisphere continues to inhibit the lesioned side, which leads to suppressed brain activation. This imbalance of activation is mitigated postrecovery, yet this phenomenon can persist for years.[82] After a period of VR-based rehabilitation, a shift of activation from the contralesional to ipsilesional SM1 reflects improved interhemispheric balance. This pattern is consistent with the findings of previous studies in terms of physical therapy-induced neural plasticity.[83,84] Carey et al[85] demonstrated that, after a period of intensive finger tracking training, there was a reversion from the contralesional control to the normal ipsilesional control of the affected hand motion. This reorganization pattern parallels with motor recovery.[86] VR-induced neural plasticity identified in this review showed not only the consistent direction of activation shifts, but also could augment the magnitude of reorganization compared with conventional rehabilitation. Wang et al[42] and Saleh et al[36] demonstrated that VR group reached this pattern more significantly than the time-matched rehabilitation approaches (occupational therapy and robotic-based therapy). This is the most pronounced pattern, supported by 11 studies in this review, with 2 RCTs and 1 CCT, and all studies have good to fair quality. Further clinical trials are still warranted to confirm and clarify this phenomenon.

Enhanced cortical connectivity

VR-induced neural plasticity was also revealed through connectivity analysis from a network-level view. In this systematic review, 4 studies showed the improvement of connectivity in the motor network, and 1 study showed improvement in the dorsal attention network. Using a VR intervention for motor deficits, increased functional connectivity was found between ipsilesional M1 and bilateral SM1,[38] SMA,[35] contralesional M1, bilateral S1, ipsilesional superior parietal gyrus, and cerebellum.[45] Improvement in effective connectivity showed facilitation of M1 by S1,[36,45] and was positively correlated to behavior outcomes. After stroke insult, both the focal damage and the disturbance of the neural network contribute to the deficits. These detrimental effects of the lesion go beyond the anatomic site: the remote areas could also be affected[87] and the abnormal connectivity could be persistent. The intra- and inter-hemispheric connectivity between the ipsilesional M1 and other areas is disturbed due to stroke. Rehme et al[88] found the positive coupling of ipsilesional SMA and PMC with ipsilesional M1 was reduced in patients with acute stroke. For subacute patients, the functional connectivity between ipsilesional SMA and M1, and interhemispheric coupling of both SMAs was reduced.[89] In patients with chronic stroke, decreased connectivity of ipsilesional M1 with contralesional SM1, bilateral SMA, inferior parietal lobule was found.[90] The treatment-induced plasticity showed improvement in connectivity. James et al[91] found that, after 3 weeks of upper extremity rehabilitation, the motor network effective connectivity was improved by the increased facilitation of bilateral PMC to ipsilesional M1. Fan et al[92] found 4 weeks robotic rehabilitation elicited increased functional connectivity between ipsilesional M1 and contralesional M1, bilateral PFC, and cerebellum. The increased connectivity between ipsilesional M1 and contralesional M1, medial superior frontal gyrus was reported after rehabilitation.[90]

Increased activation of frontal lobe

Four studies reported an increased activation of frontal lobe after VR intervention. Two EEG studies, RCTs with good quality, found increased concentration and brain activity in the frontopolar and frontal areas[32] and increased fronto-central cortical activations.[28] Two fMRI studies found increased prefrontal cortex activation.[21,50] The increased activation of this region after VR intervention might reflect the compensatory cortical reorganization, in which the nonmotor areas are adaptively engaged with motor function recovery. Overactivation of PFC in the chronic stage of stroke recovery found in other studies indicated the engagement of the executive process in performing motor task and the involvement of attention resources.[93,94] For VR intervention targeted at the neglect training,[50] the increased task-related brain activity at the PFC related to the goal-directed behavior and complex cognitive processing. The PFC was also found to modulate the neuronal network associated with the experience of presence in the VR environment,[95] and it could be activated in response to the external perturbation in VR balance tasks involving attention.[96,97]

Expansion of TMS mapping

The expansion of TMS affected hand muscle representations[3,47,49] and improved symmetry of corticomotor excitability[30] was reported after VR intervention. Significant correlations were found between the TMS mapping area and the functional outcomes.[49] With the progression of the motor recovery and increased use of the affected limb, expansion of TMS mapping reflects the use-dependent plasticity. This reorganization pattern was also consistently found in previous studies, and the treatment protocol included constraint-induced movement therapy, conventional rehabilitation, bilateral arm training, and task-oriented training.[73] The improvement presented in the TMS mapping is positively correlated to behavior outcomes and this brain plasticity measure could be used as a biomarker for functional recovery.[74]

The involvement of mirror neuron system

The involvement of mirror neuron system reveals the possible specific neural mechanisms of VR. The core mirror neuron system in human includes the inferior parietal lobule, ventral premotor cortex, and inferior frontal gyrus; it is more like a functionally distributed network involving the primary and secondary motor areas rather than specific separate regions.[98] In recent decades, the concept of the mirror neuron system has brought insights on neurorehabilitation. Motor observation, imitation and imagery could activate similar circuits as execution, providing effective surrogates for the motor recovery approaches. The concept of mirror neuron system was also integrated into the design and development of VR system.[99] The avatar in the virtual environment serves as the external representative of the user, so during VR training the patients are not only performing motor tasks, but also observe and imitate the motions with the augmented feedback information over the real environment. As shown in table 2, several VR systems in the included studies used the avatar presentation as therapeutic advantages. Additionally, "learning by imitation" could be enhanced in the virtual environment by the facilitation of the direct input to M1 via mirror neuron.[100] A study[101] showed that the action observation system, as supported by the mirror neuron concept during hand motion observation, imagery and imitation could be elicited by the VR system.

Study limitations

This systematic review has several limitations. First, only 9 controlled trials (7 RCTs and 2 CCTs) were selected and suggested the difference of neural plasticity outcomes between VR intervention and conventional rehabilitation. The remaining 18 studies did not have control group; thus, the results were presented as pre-post changes occurred with VR. Second, most studies had a small sample size, which limited the generalization and undermined the reliability of the findings. It also hampered the ability to perform correlation analysis between neural plasticity and functional outcomes. Third, the heterogeneity of VR paradigms and neural plasticity measures are high, which made it difficult to draw conclusions about VR-specific neural plasticity effects based on current information. Further VR system development with standardized neuroimaging measures should be considered to investigate VR-specific neural plasticity. Neural plasticity in stroke recovery is complex. The underlying mechanism could depend on many clinical factors including lesion type, location, severity, and stroke chronicity. Many included studies did not classify patients based on these essential factors, which could increase bias. In addition, for therapeutic advantages of each VR system summarized in table 2, it should be clarified that the included studies may not provide all details of VR intervention and these advantages were extracted by the corresponding authors. Some systems may possess more beneficial features implementing neurorehabilitation principles that were not reported and detected. Lastly, this review included studies that have more than 1 mechanism beyond VR to improve neural plasticity, and it could confound the results. The neural plasticity measurements we cited have a wide range of outcomes regarding their sensitivity and specificity with regards to clinical outcomes,[102] which has limited their use in the clinical setting.

Future Research

We recommend future research should focus on the design of high-quality RCTs with larger sample size focusing on influence of VR on neural organization with the aim to detect the VR specific effect on neural plasticity. The use of active control is favored, because it matched the treatment time received in both groups and eliminate the potential confounding. Great homogeneity in terms of patient's characteristics should be achieved to control the intersubject variations. Adequate follow-up evaluations after intervention could aid elucidate the long-term effects of VR. The design and selection of VR systems should consider the therapeutic advantages, and studies should report VR intervention protocol in detail to help identify the specific effects of VR.

Conclusions

VR-induced changes in neural plasticity for survivors of stroke; these changes reflected the neural substrates of restoration and compensation of functional deficits. The positive correlation between neural plasticity changes and functional recovery elucidates the mechanisms of the therapeutic effects of VR in stroke rehabilitation. It should be noted that only a few included studies were RCTs with adequate sample size, and because VR is not a universal intervention regimen, more studies in this field are warranted with the consideration of differences in VR system. This review prompts the systematic understanding of the neurophysiological mechanisms of VR-based stroke rehabilitation and summarizes the emerging evidence for ongoing innovation of VR system and its application in stroke rehabilitation.

Keywords

Neuroimaging; Neuronal plasticity; Rehabilitation; Stroke rehabilitation; Virtual reality

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Medline via Ebsco search strategy

(MH "Neuronal Plasticity+") OR TI (neuroplastic* OR ((Remap* OR re-map* OR re-organiz* OR re-organis* OR reorganiz* OR reorganis* OR plastic*) N10 (brain OR cerebral OR frontal OR temporal OR parietal OR occipital OR cortex OR cortical OR synap* OR neural OR interneuronal OR inter-neuronal OR brainstem* OR pons OR medulla* OR midbrain* OR cerebell* OR cerebrum* OR trigeminal OR limbic OR frontal OR prefrontal OR occipital OR temporal OR amyg* OR epithal* OR hippocamp* OR Hypothal* OR olfactor* OR parahippocamp* OR broca OR dentate OR cingul* OR neocort* OR entorhinal OR piriform OR parietal OR Wernicke OR activity-dependent))) OR AB (neuroplastic* OR ((Remap* OR re-map* OR re-organiz* OR re-organis* OR reorganiz* OR reorganis* OR plastic*) N10 (brain OR cerebral OR frontal OR temporal OR parietal OR occipital OR cortex OR cortical OR synap* OR neural OR interneuronal OR inter-neuronal OR brainstem* OR pons OR medulla* OR midbrain* OR cerebell* OR cerebrum* OR trigeminal OR limbic OR frontal OR prefrontal OR occipital OR temporal OR amyg* OR epithal* OR hippocamp* OR Hypothal* OR olfactor* OR parahippocamp* OR broca OR dentate OR cingul* OR neocort* OR entorhinal OR piriform OR parietal OR Wernicke OR activity-dependent)))

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(MH "Stroke+") OR AB ((stroke* OR "hemorrhagic stroke" OR "transient ischemic attack" OR "acute ischemic stroke" OR CVA* OR "cerebral vascular accident" OR "cerebrovascular accident" OR "cerebral vascular accidents" OR "cerebrovascular accidents" OR ((brain* OR brainstem* OR pons OR medulla* OR midbrain* OR cerebell* OR cerebrum* OR cerebral OR trigeminal OR limbic OR frontal OR prefrontal OR occipital OR temporal OR amyg* OR epithal* OR hippocamp* OR Hypothal* OR olfactor* OR parahippocamp* OR broca OR dentate OR cingul* OR neocort* OR entorhinal OR piriform OR parietal OR wernicke OR "motor cortex" OR "sensorimotor cortex" OR "olfactory cortex" OR "auditory cortex" OR "visual cortex") AND (ischem* OR ischaem* OR embol* OR thrombo* OR thrombotic OR thrombosis OR thromboses OR thrombi OR thrombus OR hemorrhag* OR haemorrhag* OR bleed* OR infarc* OR necro*)))) AND TI ((stroke* OR "hemorrhagic stroke" OR "transient ischemic attack" OR "acute ischemic stroke" OR CVA* OR "cerebral vascular accident" OR "cerebrovascular accident" OR "cerebral vascular accidents" OR "cerebrovascular accidents" OR ((brain* OR brainstem* OR pons OR medulla* OR midbrain* OR cerebell* OR cerebrum* OR cerebral OR trigeminal OR limbic OR frontal OR prefrontal OR occipital OR temporal OR amyg* OR epithal* OR hippocamp* OR Hypothal* OR olfactor* OR parahippocamp* OR broca OR dentate OR cingul* OR neocort* OR entorhinal OR piriform OR parietal OR wernicke OR "motor cortex" OR "sensorimotor cortex" OR "olfactory cortex" OR "auditory cortex" OR "visual cortex") AND (ischem* OR ischaem* OR embol* OR thrombo* OR thrombotic OR thrombosis OR thromboses OR thrombi OR thrombus OR hemorrhag* OR haemorrhag* OR bleed* OR infarc* OR necro*))))

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PsycInfo search strategy

DE "Brain Training" OR DE "Brain Stimulation" OR DE "Neural Plasticity" OR TI (neuroplastic* OR ((Remap* OR re-map* OR re-organiz* OR re-organis* OR reorganiz* OR reorganis* OR plastic*) N10 (brain OR cerebral OR frontal OR temporal OR parietal OR occipital OR cortex OR cortical OR synap* OR neural OR interneuronal OR inter-neuronal OR brainstem* OR pons OR medulla* OR midbrain* OR cerebell* OR cerebrum* OR trigeminal OR limbic OR frontal OR prefrontal OR occipital OR temporal OR amyg* OR epithal* OR hippocamp* OR Hypothal* OR olfactor* OR parahippocamp* OR broca OR dentate OR cingul* OR neocort* OR entorhinal OR piriform OR parietal OR Wernicke OR activity-dependent))) OR AB (neuroplastic* OR ((Remap* OR re-map* OR re-organiz* OR re-organis* OR reorganiz* OR reorganis* OR plastic*) N10 (brain OR cerebral OR frontal OR temporal OR parietal OR occipital OR cortex OR cortical OR synap* OR neural OR interneuronal OR inter-neuronal OR brainstem* OR pons OR medulla* OR midbrain* OR cerebell* OR cerebrum* OR trigeminal OR limbic OR frontal OR prefrontal OR occipital OR temporal OR amyg* OR epithal* OR hippocamp* OR Hypothal* OR olfactor* OR parahippocamp* OR broca OR dentate OR cingul* OR neocort* OR entorhinal OR piriform OR parietal OR Wernicke OR activity-dependent)))

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DE "Cerebrovascular Accidents" OR DE "Cerebral Ischemia" OR AB ((stroke* OR "hemorrhagic stroke" OR "transient ischemic attack" OR "acute ischemic stroke" OR CVA* OR "cerebral vascular accident" OR "cerebrovascular accident" OR "cerebral vascular accidents" OR "cerebrovascular accidents" OR ((brain* OR brainstem* OR pons OR medulla* OR midbrain* OR cerebell* OR cerebrum* OR cerebral OR trigeminal OR limbic OR frontal OR prefrontal OR occipital OR temporal OR amyg* OR epithal* OR hippocamp* OR Hypothal* OR olfactor* OR parahippocamp* OR broca OR dentate OR cingul* OR neocort* OR entorhinal OR piriform OR parietal OR wernicke OR "motor cortex" OR "sensorimotor cortex" OR "olfactory cortex" OR "auditory cortex" OR "visual cortex") AND (ischem* OR ischaem* OR embol* OR thrombo* OR thrombotic OR thrombosis OR thromboses OR thrombi OR thrombus OR hemorrhag* OR haemorrhag* OR bleed* OR infarc* OR necro*)))) AND TI ((stroke* OR "hemorrhagic stroke" OR "transient ischemic attack" OR "acute ischemic stroke" OR CVA* OR "cerebral vascular accident" OR "cerebrovascular accident" OR "cerebral vascular accidents" OR "cerebrovascular accidents" OR ((brain* OR brainstem* OR pons OR medulla* OR midbrain* OR cerebell* OR cerebrum* OR cerebral OR trigeminal OR limbic OR frontal OR prefrontal OR occipital OR temporal OR amyg* OR epithal* OR hippocamp* OR Hypothal* OR olfactor* OR parahippocamp* OR broca OR dentate OR cingul* OR neocort* OR entorhinal OR piriform OR parietal OR wernicke OR "motor cortex" OR "sensorimotor cortex" OR "olfactory cortex" OR "auditory cortex" OR "visual cortex") AND (ischem* OR ischaem* OR embol* OR thrombo* OR thrombotic OR thrombosis OR thromboses OR thrombi OR thrombus OR hemorrhag* OR haemorrhag* OR bleed* OR infarc* OR necro*))))

AND

DE "Virtual Reality" OR DE "Augmented Reality" OR DE "Virtual Reality Exposure Therapy" OR TI (“virtual reality” OR VR OR "augmented reality" OR "mixed reality" OR “virtual environment” OR “video game” OR “video games” OR gaming) OR AB (“virtual reality” OR VR OR "augmented reality" OR "mixed reality" OR “virtual environment” OR “video game” OR “video games” OR gaming)

CINAHL search strategy

(MH "Neuronal Plasticity") OR TI ((neuroplastic* OR ((Remap* OR re-map* OR re-organiz* OR re-organis* OR reorganiz* OR reorganis* OR plastic*) N10 (brain OR cerebral OR frontal OR temporal OR parietal OR occipital OR cortex OR cortical OR synap* OR neural OR interneuronal OR inter-neuronal OR brainstem* OR pons OR medulla* OR midbrain* OR cerebell* OR cerebrum* OR trigeminal OR limbic OR frontal OR prefrontal OR occipital OR temporal OR amyg* OR epithal* OR hippocamp* OR Hypothal* OR olfactor* OR parahippocamp* OR broca OR dentate OR cingul* OR neocort* OR entorhinal OR piriform OR parietal OR Wernicke OR activity-dependent)))) OR AB ((neuroplastic* OR ((Remap* OR re-map* OR re-organiz* OR re-organis* OR reorganiz* OR reorganis* OR plastic*) N10 (brain OR cerebral OR frontal OR temporal OR parietal OR occipital OR cortex OR cortical OR synap* OR neural OR interneuronal OR inter-neuronal OR brainstem* OR pons OR medulla* OR midbrain* OR cerebell* OR cerebrum* OR trigeminal OR limbic OR frontal OR prefrontal OR occipital OR temporal OR amyg* OR epithal* OR hippocamp* OR Hypothal* OR olfactor* OR parahippocamp* OR broca OR dentate OR cingul* OR neocort* OR entorhinal OR piriform OR parietal OR Wernicke OR activity-dependent))))

AND

((MH "Stroke+") OR (MH "Stroke Patients")) OR (AB ((stroke* OR "hemorrhagic stroke" OR "transient ischemic attack" OR "acute ischemic stroke" OR CVA* OR "cerebral vascular accident" OR "cerebrovascular accident" OR "cerebral vascular accidents" OR "cerebrovascular accidents" OR ((brain* OR brainstem* OR pons OR medulla* OR midbrain* OR cerebell* OR cerebrum* OR cerebral OR trigeminal OR limbic OR frontal OR prefrontal OR occipital OR temporal OR amyg* OR epithal* OR hippocamp* OR Hypothal* OR olfactor* OR parahippocamp* OR broca OR dentate OR cingul* OR neocort* OR entorhinal OR piriform OR parietal OR wernicke OR "motor cortex" OR "sensorimotor cortex" OR "olfactory cortex" OR "auditory cortex" OR "visual cortex") AND (ischem* OR ischaem* OR embol* OR thrombo* OR thrombotic OR thrombosis OR thromboses OR thrombi OR thrombus OR hemorrhag* OR haemorrhag* OR bleed* OR infarc* OR necro*)))) OR TI ((stroke* OR "hemorrhagic stroke" OR "transient ischemic attack" OR "acute ischemic stroke" OR CVA* OR "cerebral vascular accident" OR "cerebrovascular accident" OR "cerebral vascular accidents" OR "cerebrovascular accidents" OR ((brain* OR brainstem* OR pons OR medulla* OR midbrain* OR cerebell* OR cerebrum* OR cerebral OR trigeminal OR limbic OR frontal OR prefrontal OR occipital OR temporal OR amyg* OR epithal* OR hippocamp* OR Hypothal* OR olfactor* OR parahippocamp* OR broca OR dentate OR cingul* OR neocort* OR entorhinal OR piriform OR parietal OR wernicke OR "motor cortex" OR "sensorimotor cortex" OR "olfactory cortex" OR "auditory cortex" OR "visual cortex") AND (ischem* OR ischaem* OR embol* OR thrombo* OR thrombotic OR thrombosis OR thromboses OR thrombi OR thrombus OR hemorrhag* OR haemorrhag* OR bleed* OR infarc* OR necro*)))))

AND

((MH "Virtual Reality+") OR (MH "Virtual Reality Exposure Therapy")) OR (TI (“virtual reality” OR VR OR "augmented reality" OR "mixed reality" OR “virtual environment” OR “video game” OR “video games” OR gaming) OR AB (“virtual reality” OR VR OR "augmented reality" OR "mixed reality" OR “virtual environment” OR “video game” OR “video games” OR gaming))

Embase search strategy

((brain OR cerebral OR frontal OR temporal OR occipital OR cortex OR synap* OR neural OR interneuronal OR 'inter neuronal' OR brainstem* OR pons OR medulla* OR midbbrain* OR cerebell* OR cerebrum* OR trigeminal OR limbic OR olfactor* OR parahippocamp* OR broca OR dentate OR cingul* OR neocort* OR entorhinal OR piriform OR parietal OR wernicke OR 'actvity dependent') NEAR/10 (neuroplastic* OR remap* OR 're map*' OR reorganiz* OR 're organiz*' OR reorganis* OR 're organis*' OR plastic*)):ti,ab OR 'nerve cell plasticity'/exp/mj

AND

'brain ischemia'/exp/mj OR 'cerebrovascular accident'/exp/mj OR stroke*:ti,ab OR 'hemorrhagic stroke':ti,ab OR 'transient ischemic attack':ti,ab OR 'acute ischemic stroke':ti,ab OR cva*:ti,ab OR 'cerebral vascular accident':ti,ab OR 'cerebrovascular accident':ti,ab OR 'cerebral vascular accidents':ti,ab OR 'cerebrovascular accidents':ti,ab OR ((brain*:ti,ab OR brainstem*:ti,ab OR pons:ti,ab OR medulla*:ti,ab OR midbrain*:ti,ab OR cerebell*:ti,ab OR cerebrum*:ti,ab OR cerebral:ti,ab OR trigeminal:ti,ab OR limbic:ti,ab OR frontal:ti,ab OR prefrontal:ti,ab OR occipital:ti,ab OR temporal:ti,ab OR amyg*:ti,ab OR epithal*:ti,ab OR hippocamp*:ti,ab OR hypothal*:ti,ab OR olfactor*:ti,ab OR parahippocamp*:ti,ab OR broca:ti,ab OR dentate:ti,ab OR cingul*:ti,ab OR neocort*:ti,ab OR entorhinal:ti,ab OR piriform:ti,ab OR parietal:ti,ab OR wernicke:ti,ab OR 'motor cortex':ti,ab OR 'sensorimotor cortex':ti,ab OR 'olfactory cortex':ti,ab OR 'auditory cortex':ti,ab OR 'visual cortex':ti,ab) AND (ischem*:ti,ab OR ischaem*:ti,ab OR embol*:ti,ab OR thrombo*:ti,ab OR thrombotic:ti,ab OR thrombosis:ti,ab OR thromboses:ti,ab OR thrombi:ti,ab OR thrombus:ti,ab OR hemorrhag*:ti,ab OR haemorrhag*:ti,ab OR bleed*:ti,ab OR infarc*:ti,ab OR necro*:ti,ab))

AND

'virtual reality'/exp/mj OR 'virtual reality exposure therapy'/exp/mj OR 'virtual reality head mounted display'/exp/mj OR 'virtual reality':ti,ab OR vr:ti,ab OR 'augmented reality':ti,ab OR 'mixed reality':ti,ab OR 'virtual environment':ti,ab OR 'video game':ti,ab OR 'video games':ti,ab OR gaming:ti,ab

IEEE XPlore Digital Library search strategy

(((Document Title:"virtual reality" OR VR OR "augmented reality" OR "mixed reality" OR "virtual environment" OR "video game" OR gaming OR "video games") OR Abstract:"virtual reality" OR VR OR "augmented reality" OR "mixed reality" OR "virtual environment" OR "video game" OR gaming OR "video games")))

AND

((All Metadata:stroke OR "brain ischemia" OR "ischemic attack" OR "cerebrovascular accident" OR "hemorrhagic stroke" OR "transient ischemic attack" OR "acute ischemic stroke" OR "cerebral vascular accident")))

AND

(((Document Title:"brain plasticity" OR "neuronal plasticity" OR "neural plasticity" OR "nerve cell plasticity" OR "synaptic plasticity" OR "brain remapping" OR "brain reorganiziation" OR "brain reorganisation" OR "neuronal remapping" OR "neuronal reorganisation" OR "neuronal reorganization") OR Abstract:"brain plasticity" OR "neuronal plasticity" OR "neural plasticity" OR "nerve cell plasticity" OR "synaptic plasticity" OR "brain remapping" OR "brain reorganiziation" OR "brain reorganisation" OR "neuronal remapping" OR "neuronal reorganisation" OR "neuronal reorganization"))

Scopus search strategy

((TITLE (neuroplasticiy OR neuroplastic OR "neuronal plasticity" OR "nerve cell plasticity" OR "synaptic plasticity" OR "brain remapping" OR "brain remap" OR "neruonal remapping" OR "synaptic remapping") OR ABS (neuroplasticiy OR neuroplastic OR "neuronal plasticity" OR "nerve cell plasticity" OR "synaptic plasticity" OR "brain remapping" OR "brain remap" OR "neuronal remapping" OR "synaptic remapping")))

AND

(((ABS (brain* OR brainstem* OR pons OR medulla* OR midbrain* OR cerebell* OR cerebrum* OR cerebral OR trigeminal OR limbic OR frontal OR prefrontal OR occipital OR temporal OR amyg* OR epithal* OR hippocamp* OR hypothal* OR olfactor* OR parahippocamp* OR broca) OR ABS (dentate OR cingul* OR neocort* OR entorhinal OR piriform OR parietal OR wernicke OR 'motor AND cortex' OR 'sensorimotor AND cortex' OR 'olfactory AND cortex' OR 'auditory AND cortex' OR 'visual AND cortex') W/10 (ischem* OR ischaem* OR embol* OR thrombo* OR thrombotic OR thrombosis OR thromboses OR thrombi OR thrombus OR hemorrhag* OR haemorrhag* OR bleed* OR infarc* OR necro*))) OR ((TITLE (stroke OR "brain ischemia"

OR "ischemic attack" OR "cerebrovascular accident" OR "hemorrhagic stroke" OR "transient ischemic attack" OR "acute ischemic stroke" OR "cerebral vascular accident") OR ABS (stroke OR "brain ischemia" OR "ischemic attack" OR "cerebrovascular accident" OR "hemorrhagic stroke" OR "transient ischemic attack" OR "acute ischemic stroke" OR "cerebral vascular accident"))))

AND

((TITLE ("virtual reality" OR vr OR "augmented reality" OR "mixed reality" OR "virtual environment" OR "video game" OR "video games" OR gaming) OR ABS ("virtual reality" OR vr OR "augmented reality" OR "mixed reality" OR "virtual environment" OR "video game" OR "video games" OR gaming)))

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