

Neurorrehabilitación Digital: Realidad Virtual, Robótica y Neuroplasticidad Después del Accidente Cerebrovascular

Digital Neurorehabilitation: Virtual Reality, Robotics and Neuroplasticity After Stroke

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RESUMEN

El accidente cerebrovascular constituye una de las principales causas de discapacidad neurológica prolongada y frecuentemente produce alteraciones motoras persistentes, pérdida de independencia y limitaciones en la participación social. La realidad virtual y la rehabilitación asistida por robots han surgido como estrategias para incrementar la intensidad, repetición y especificidad del tratamiento, así como la retroalimentación y participación del paciente. El objetivo de este estudio fue analizar su efectividad para promover la neuroplasticidad y mejorar los resultados motores y funcionales en adultos después de un accidente cerebrovascular. Se realizó una revisión integrativa estructurada basada en el método científico y en los principios de PRISMA 2020 mediante búsquedas en PubMed/MEDLINE, Cochrane Library, Scopus, Web of

Science, IEEE Xplore, PEDro y bases oficiales de revistas científicas. Se seleccionaron 20 publicaciones, entre ellas revisiones sistemáticas, metaanálisis, ensayos controlados aleatorizados, revisiones narrativas y una guía de práctica clínica. Diez publicaciones fueron revisiones sistemáticas o metaanálisis; cinco presentaron resultados predominantemente favorables, cuatro hallazgos condicionados o mixtos y una no demostró un beneficio adicional claro. La realidad virtual se asoció con mejoras seleccionadas en la función motora del miembro superior, destreza, independencia funcional, calidad de vida, activación cortical y conectividad funcional. La rehabilitación robótica proporcionó práctica intensiva y medible y mejoró algunos resultados motores, aunque su superioridad frente a la rehabilitación convencional con dosis equivalentes fue inconsistente. Las mejoras en control motor y fuerza no siempre se tradujeron en mayor independencia o utilización espontánea del miembro afectado. La neurorrehabilitación digital mostró mayor utilidad cuando proporcionó entrenamiento activo, repetitivo, intensivo, específico, progresivo y acompañado de retroalimentación. Estas tecnologías deben integrarse como complementos de la rehabilitación convencional y no como sustitutos universales.

PALABRAS CLAVE

Accidente cerebrovascular; neurorrehabilitación; realidad virtual; robótica; neuroplasticidad; recuperación motora; independencia funcional.

ABSTRACT

Stroke is a leading cause of long-term neurological disability, frequently producing persistent motor impairment, loss of independence, and limitations in social participation. Virtual reality and robot-assisted rehabilitation have emerged as strategies for increasing treatment intensity, repetition, task specificity, feedback, and patient engagement. This study aimed to analyze their effectiveness in promoting neuroplasticity and improving motor and functional outcomes in adults after stroke. A structured integrative literature review based on the Scientific Method and PRISMA 2020 principles was conducted using PubMed/MEDLINE, the Cochrane Library, Scopus, Web of Science, IEEE Xplore, PEDro, and official journal databases. Twenty publications were selected, including systematic reviews, meta-analyses, randomized controlled trials, narrative reviews, and a clinical practice guideline. Ten publications were systematic reviews or meta-analyses; five presented predominantly favorable findings, four reported conditional or mixed results, and one found no clear additional benefit. Virtual reality was associated with selected improvements in upper-limb motor function, dexterity, functional independence, quality of life, cortical activation, and functional connectivity. Robot-assisted rehabilitation provided intensive and measurable movement practice and improved selected impairment-based outcomes, although its superiority over dose-matched conventional rehabilitation was inconsistent. Improvements in motor control and strength did not always translate into greater independence or spontaneous use of the affected limb in daily life. The findings indicate that digital neurorehabilitation is most effective when it provides active, repetitive, intensive, task-specific, progressively challenging, and feedback-rich training. Virtual reality and robotics should be integrated as complementary components of conventional rehabilitation rather than universal replacements. Further randomized trials with standardized protocols, equivalent treatment doses, clinically meaningful outcomes, direct neuroplasticity measurements, safety assessment, and long-term follow-up are required.

KEYWORDS

Stroke; neurorehabilitation; virtual reality; robotics; neuroplasticity; motor recovery; functional independence.

INTRODUCCIÓN

Stroke remains one of the leading causes of death and long-term disability worldwide, and a substantial proportion of survivors experience persistent motor, sensory, cognitive, and functional limitations that interfere with independence and social participation. Although advances in acute stroke care have improved survival, these achievements have also increased the number of individuals living with chronic neurological deficits and requiring long-term rehabilitation. Upper-limb weakness, impaired manual dexterity, postural instability, gait dysfunction, spasticity, and reduced ability to perform activities of daily living are among the most disabling consequences of stroke. These impairments may

persist even after patients complete conventional rehabilitation programs, illustrating the continuing gap between neurological recovery and meaningful functional reintegration (Langhorne et al., 2011; Winstein et al., 2016).

Conventional stroke rehabilitation generally combines physical therapy, occupational therapy, task-specific practice, compensatory strategies, and functional training. These interventions remain essential components of care; however, their effectiveness may be limited by insufficient treatment intensity, reduced opportunities for repetition, difficulties maintaining patient motivation, variability in therapist availability, and restricted access to specialized rehabilitation services. Motor recovery requires the repeated and progressive practice of meaningful tasks, yet healthcare systems frequently struggle to provide the frequency and duration of therapy necessary to maximize experience-dependent neuroplasticity. Consequently, there is increasing interest in digital and technology-assisted interventions capable of expanding rehabilitation intensity while maintaining individualized feedback, objective assessment, and patient engagement (Langhorne et al., 2011; Winstein et al., 2016).

Neuroplasticity provides the biological foundation for post-stroke recovery. It refers to the nervous system's capacity to modify its structure, function, connectivity, and patterns of activation in response to injury, experience, and training. Following a stroke, recovery may involve the reorganization of surviving neural networks, changes in cortical excitability, recruitment of secondary motor areas, strengthening of residual corticospinal pathways, synaptic remodeling, and modifications in interhemispheric interactions. These processes are particularly active during the early post-stroke period but may continue during the chronic stage when appropriately intensive, specific, and meaningful training is provided (Dimyan & Cohen, 2011; Di Pino et al., 2014).

Post-stroke plasticity is not inherently beneficial. Adaptive plasticity may facilitate restitution of impaired functions or the development of effective compensatory strategies, whereas maladaptive plasticity may reinforce abnormal movement patterns, excessive reliance on the unaffected limb, inefficient compensations, pain, spasticity, or learned non-use of the affected extremity. Rehabilitation must therefore promote neural changes that are associated with functional improvement rather than simply increasing cerebral activation. The relationship between plasticity and recovery is influenced by lesion location, lesion volume, corticospinal tract integrity, time since stroke, initial motor impairment, age, comorbidities, cognitive status, emotional health, genetic factors, treatment intensity, and the characteristics of the training task (Di Pino et al., 2014; Li, 2017; Mang et al., 2013).

Experience-dependent neuroplasticity is strongly associated with repetition, task specificity, progressive difficulty, active participation, sensory feedback, motivation, and the salience of training. These principles explain why digital technologies have become increasingly relevant to contemporary neurorehabilitation. Virtual reality and robotic systems can deliver highly repetitive and standardized exercises while providing real-time visual, auditory, haptic, or performance-based feedback. They may also allow therapists to modify task complexity, assistance, resistance, movement range, and treatment intensity according to each patient's capabilities. In this context, technology is not intended to replace conventional therapy or clinical judgment but to expand the amount, precision, adaptability, and measurability of rehabilitation (Krakauer et al., 2012; Mang et al., 2013).

Virtual reality refers to computer-generated environments that allow users to interact with simulated objects, tasks, or scenarios. Depending on the system, virtual reality can be non-immersive, semi-immersive, or fully immersive. Non-immersive applications generally use conventional screens, cameras, motion sensors, or commercial gaming devices, whereas immersive systems use head-mounted displays and motion-tracking technology to create a stronger sense of presence. In stroke rehabilitation, these environments may be used to practice reaching, grasping, object manipulation, balance, gait, spatial orientation, dual-task performance, and activities resembling real-world situations.

One of the principal advantages of virtual reality is its capacity to transform repetitive exercises into interactive, goal-directed tasks. Gamified feedback may increase attention, motivation, adherence, and active participation, all of which are relevant to motor learning. Virtual environments can also simulate activities that would be difficult, unsafe, or expensive to reproduce in a conventional clinical setting. Furthermore, performance data can be collected continuously, allowing the quantification of movement accuracy, speed, range, trajectory, task completion, and progression over time. These characteristics make virtual reality a promising instrument for both therapeutic intervention and functional assessment.

Evidence regarding the effectiveness of virtual reality has grown substantially. Earlier research demonstrated that virtual reality training could be associated with changes in cortical activation and locomotor recovery, suggesting that its effects may extend beyond improvements in task performance. In an experimenter-blinded randomized study, You et al. (2005) reported virtual reality-associated cortical reorganization and improved locomotor outcomes in individuals with chronic stroke. Although this early study involved a limited sample and must be interpreted cautiously, it provided an important foundation for investigating the neural mechanisms underlying virtual rehabilitation.

More recent research has examined whether functional improvements produced by virtual reality correspond to measurable indicators of neuroplasticity. Hao et al. (2022), in a systematic review, found that virtual reality interventions were associated with changes in brain activation, cortical reorganization, connectivity, and other neurophysiological indicators. The authors also identified positive relationships between neural changes and functional recovery. However, the included studies differed considerably in intervention protocols, neurological measurements, stroke chronicity, and patient characteristics, limiting the certainty and generalizability of the findings.

Biological markers have also been incorporated into virtual reality research. Huang et al. (2022) evaluated immersive virtual reality motor training in people with chronic stroke and examined functional outcomes alongside serum biomarkers related to inflammation, oxidative stress, and neuroplasticity. The intervention was associated with improvements in several upper-limb outcomes, although differences between virtual reality and conventional therapy were not consistent across all biomarkers and clinical measures. These findings illustrate both the potential of immersive training and the need for larger trials capable of establishing whether biological changes mediate clinically meaningful recovery.

Systematic reviews and meta-analyses generally indicate that virtual reality can improve selected motor and functional outcomes, particularly when it is used as an adjunct to conventional therapy and increases the total amount of rehabilitation. Soleimani et al. (2024) analyzed virtual reality interventions for upper-limb rehabilitation and reported benefits in motor function, functional independence, dexterity, spasticity, and quality of life. Nevertheless, the magnitude of the effect varied according to immersion level, intervention duration, outcomes, and time since stroke. Similarly, the updated Cochrane review by Laver et al. (2025) emphasizes that virtual reality may provide additional benefits for some outcomes, while also highlighting substantial heterogeneity across technologies, treatment doses, comparator interventions, and study quality. Therefore, the current evidence supports cautious clinical integration rather than the assumption that all virtual reality systems are equally effective.

Robotic rehabilitation represents another major component of digital neurorehabilitation. Rehabilitation robots include end-effector devices, exoskeletons, wearable systems, robotic gloves, portable devices, and gait-training platforms. These systems may assist, guide, resist, or measure movement according to the patient's residual motor capacity. Some devices provide passive movement for individuals with severe weakness, whereas others use active-assisted or active-resisted modes that require voluntary participation. Robotic systems may therefore enable patients to complete a greater number of movement repetitions with consistent trajectories and quantifiable performance parameters.

Robot-assisted therapy is particularly relevant to upper-limb rehabilitation because recovery of the arm and hand commonly remains incomplete after stroke. The complexity of reaching, grasping, object manipulation, and fine motor control makes upper-extremity rehabilitation demanding for both patients and therapists. Robots can deliver intensive and reproducible training, but their clinical value depends on whether practiced movements transfer to activities of daily living. Improvements measured only through device-specific exercises or impairment scales may not necessarily translate into spontaneous use of the affected limb in real-world contexts.

Evidence from systematic reviews supports modest benefits of robot-assisted upper-limb therapy, but conclusions are not uniform. Bertani et al. (2017) found positive effects on arm recovery, while Veerbeek et al. (2017) reported that robot-assisted therapy could improve motor control and muscle strength, although the clinical relevance and superiority over dose-matched conventional therapy remained uncertain. Chien et al. (2020) similarly concluded that robot-assisted interventions in subacute stroke could produce benefits, but outcomes depended on treatment characteristics and comparison conditions. These findings suggest that robotic therapy may be most useful as a method for increasing structured practice rather than as an isolated replacement for therapist-directed functional training.

The type and portability of the robotic system may also influence its accessibility and effectiveness. Traditional rehabilitation robots are often costly, large, and restricted to specialized facilities. Portable and wearable devices could facilitate decentralized treatment, home-based practice, and continuity of care after hospital discharge. Tseng et al. (2024) found that portable upper-limb robots may improve motor function and activities of daily living, but the available evidence remains limited by small samples, differences among devices, and inconsistent intervention protocols. Thus, portability may address access barriers, but it does not eliminate the need for clinical supervision, appropriate patient selection, and standardized outcome evaluation.

The combination of robotics and virtual reality may offer complementary advantages. Robotics can provide physical assistance, movement guidance, resistance, and haptic feedback, while virtual reality can deliver engaging environments, meaningful goals, and multisensory feedback. When integrated, these technologies may create a closed-loop rehabilitation system in which movement is continuously measured and the difficulty or assistance level is adjusted according to performance. Zhang et al. (2023) compared robot-assisted training, virtual reality, combined interventions, and conventional therapy through a network meta-analysis. Their findings suggested that combined approaches may provide advantages for balance, while virtual reality may be particularly helpful for daily function. Nevertheless, the rankings were based on heterogeneous studies, and additional direct comparisons are required before definitive conclusions can be established.

Despite encouraging results, several uncertainties continue to prevent the routine and standardized implementation of digital neurorehabilitation. First, there is considerable variation in hardware, software, immersion level, robotic design, feedback modality, treatment duration, session frequency, and exercise intensity. Interventions classified under the same technological category may therefore represent substantially different therapeutic experiences. Second, many studies include small samples, short follow-up periods, and participants with relatively mild or moderate impairments, which limits the applicability of the results to people with severe motor, visual, cognitive, communicative, or perceptual deficits.

Third, improvements in impairment-based scales do not always demonstrate recovery in participation, independence, quality of life, or spontaneous use of the affected limb. Fourth, studies frequently compare technology-enhanced therapy plus usual care against usual care alone. Under these conditions, observed benefits may result from a greater total treatment dose rather than from a specific technological mechanism. Dose-matched trials are therefore necessary to distinguish the effect of the technology from the effect of additional practice. Finally, the association between digital training and neuroplasticity remains incompletely understood because many trials measure only clinical outcomes and do not include neuroimaging, neurophysiological, biomechanical, or molecular indicators (Hao et al., 2022; Huang et al., 2022).

The timing of intervention is another unresolved issue. The early post-stroke period is characterized by enhanced biological responsiveness and rapid spontaneous recovery, but patients may also present medical instability, fatigue, reduced attention, and severe motor impairment. In the chronic phase, spontaneous recovery has slowed, yet structured training can still produce functional and neural changes. Determining whether specific digital interventions are more effective during the acute, subacute, or chronic stages is essential for establishing appropriate clinical pathways. Treatment intensity must also be individualized, since an intervention that is insufficient for one patient may cause fatigue, frustration, pain, or reduced adherence in another.

Patient-related factors further complicate implementation. Digital literacy, visual tolerance, vestibular symptoms, neglect, aphasia, cognitive impairment, cybersickness, fear of technology, and socioeconomic barriers may influence treatment acceptance and outcomes. Immersive virtual reality may not be suitable for every patient, and robotic assistance must be calibrated to avoid excessive passive participation. If a robot completes too much of the movement, the patient may perform many repetitions without generating the voluntary effort required for motor learning. Consequently, technological sophistication alone cannot guarantee neuroplastic or functional benefits.

The economic and organizational implications must also be considered. Digital rehabilitation may help address workforce shortages, expand access to therapy, and facilitate home-based follow-up; however, acquisition costs, maintenance, software updates, staff training, cybersecurity, patient privacy, technical support, and device

interoperability can restrict implementation. Evidence of statistical efficacy must therefore be complemented by studies of clinical significance, usability, cost-effectiveness, accessibility, and long-term sustainability.

Given these gaps, the present study addresses the following central research question: **To what extent do virtual reality and robot-assisted rehabilitation promote neuroplasticity and improve motor and functional outcomes in adults after stroke when compared with conventional rehabilitation?** Secondary questions examine which technological characteristics, treatment parameters, stages of recovery, and patient factors appear to influence effectiveness; whether combined virtual reality and robotic interventions provide additional benefits; and whether reported functional improvements are supported by neurophysiological or biological evidence of adaptive plasticity.

The working hypothesis is that virtual reality and robot-assisted therapy can enhance post-stroke motor recovery when they provide intensive, repetitive, task-specific, progressively challenging, and feedback-rich practice. It is further hypothesized that these technologies are most effective when integrated with conventional rehabilitation rather than implemented as isolated substitutes for therapist-guided care. A third hypothesis is that functional gains will vary according to treatment dose, time since stroke, baseline severity, degree of active participation, type of feedback, and correspondence between the trained task and real-world activities.

To address these questions, the study uses a structured integrative review design. Relevant peer-reviewed literature on adult post-stroke rehabilitation was identified through targeted searches of major biomedical and multidisciplinary databases, emphasizing PubMed/MEDLINE, the Cochrane Library, and publisher-indexed scientific sources. The review prioritizes clinical guidelines, systematic reviews, meta-analyses, randomized controlled trials, and influential neuroplasticity studies directly related to virtual reality, robotic rehabilitation, motor recovery, cortical reorganization, and functional independence. Reference selection focuses on methodological quality, relevance to the research questions, direct applicability to stroke rehabilitation, and availability of verifiable bibliographic information.

The evidence is organized into four interconnected domains: the biological principles of post-stroke neuroplasticity; the clinical effectiveness of virtual reality; the effectiveness and characteristics of robot-assisted rehabilitation; and the relationship between technological training, neural adaptation, and functional transfer. Outcomes of interest include upper- and lower-limb motor function, balance, gait, dexterity, activities of daily living, quality of life, cortical activation, functional connectivity, neurophysiological measures, and biomarkers associated with plasticity. Particular attention is given to treatment intensity, timing, immersion level, robotic assistance, patient participation, intervention duration, and comparison with dose-matched conventional therapy.

This design aligns with the research questions because it permits the integration of clinical, technological, and neurobiological evidence rather than limiting the analysis to a single outcome or device. By comparing findings across these domains, the study seeks to determine not only whether digital neurorehabilitation is effective, but also how, for whom, and under which conditions it is most likely to produce meaningful recovery. Ultimately, understanding the interaction among virtual environments, robotic assistance, motor learning, and neuroplasticity is necessary for moving from experimental technological applications toward evidence-based, individualized, and clinically sustainable stroke rehabilitation.

DESARROLLO

Stroke rehabilitation is a complex and prolonged process because neurological damage affects not only muscle strength but also motor planning, sensory integration, balance, coordination, cognition, emotional regulation, and the ability to perform activities of daily living. Recovery depends on the interaction between spontaneous biological processes and rehabilitation-induced learning. Conventional physical and occupational therapy remain the foundation of treatment; however, their results are influenced by the intensity, frequency, specificity, and duration of practice. Digital neurorehabilitation has emerged as a strategy to increase these therapeutic components through virtual reality, robotic systems, movement sensors, and computerized feedback.

Neuroplasticity as the basis of motor recovery

Neuroplasticity is the nervous system's capacity to reorganize its structure and function in response to injury and experience. After a stroke, surviving neural networks may assume part of the functions previously performed by damaged regions. This adaptation involves changes in synaptic strength, cortical excitability, interhemispheric communication, motor-network connectivity, and recruitment of secondary motor areas. Nevertheless, functional recovery does not occur automatically. Rehabilitation must provide appropriate stimuli to guide plasticity toward useful and efficient movement patterns (Dimyan & Cohen, 2011; Di Pino et al., 2014).

Motor training is more likely to stimulate adaptive plasticity when it incorporates a high number of repetitions, task-specific exercises, progressive difficulty, multisensory feedback, active participation, and meaningful goals. Conversely, insufficient practice or excessive reliance on the unaffected side may reinforce learned non-use and maladaptive compensatory patterns. Technology-assisted rehabilitation is relevant because it can systematically manipulate these motor-learning variables and document the patient's response to training (Krakauer et al., 2012; Mang et al., 2013).

Time since stroke also influences recovery. Biological plasticity is particularly active during the acute and subacute stages, although clinically relevant changes can still occur in the chronic phase. Therefore, digital interventions should not be limited to a single recovery period. Instead, their intensity and complexity should be adapted to medical stability, baseline impairment, fatigue, cognition, sensory deficits, and voluntary motor control.

Virtual reality in post-stroke rehabilitation

Virtual reality creates interactive environments in which patients perform simulated motor and functional tasks. These systems may be non-immersive, using conventional screens and motion sensors; semi-immersive, using large displays or projection systems; or fully immersive, using head-mounted displays and three-dimensional environments. Regardless of the immersion level, the therapeutic value of virtual reality depends on the quality and specificity of the activities rather than on technological novelty alone.

Virtual environments can be used to train reaching, grasping, balance, gait, postural transitions, coordination, spatial orientation, and dual-task performance. They provide immediate knowledge of results, such as scores or task-completion time, and knowledge of performance, such as information about movement direction, accuracy, speed, or range. This feedback allows patients to recognize errors and modify subsequent attempts, supporting motor learning.

Virtual reality may also increase motivation by transforming repetitive exercises into goal-directed activities. This is clinically relevant because reduced engagement can limit the intensity of long-term rehabilitation. However, gamification should not become the principal objective of treatment. A high score within a virtual task does not necessarily indicate that the patient can perform the corresponding activity independently in daily life. Therapeutic programs must therefore evaluate whether improvements transfer to real-world activities.

Evidence supports the potential of virtual reality as an adjunctive intervention. Soleimani et al. (2024) included 55 studies and 2,142 patients in a systematic review and meta-analysis of upper-limb rehabilitation. The findings indicated benefits in motor function, dexterity, functional independence, spasticity, and quality of life. The results also suggested that intervention duration, time since stroke, and level of immersion may influence effectiveness. Nevertheless, the variability among systems and treatment protocols prevents the identification of one universally superior virtual reality model.

Research has also examined the relationship between virtual rehabilitation and neuroplasticity. Hao et al. (2022) identified changes in cortical activation, functional connectivity, and other neurological measures following virtual reality interventions. These findings suggest that virtual training may modify the neural networks involved in motor control rather than producing only temporary improvements in task performance. Earlier evidence from You et al. (2005) similarly associated virtual reality training with cortical reorganization and locomotor recovery in chronic stroke.

Despite these findings, evidence of a direct causal relationship remains limited. Studies use different neuroimaging techniques, intervention doses, outcome measures, and participant populations. Some reported neural changes may

represent restitution of function, while others may reflect compensation. For this reason, improvements in cerebral activation should be interpreted together with standardized clinical and functional outcomes.

Huang et al. (2022) investigated immersive virtual reality in 30 patients with chronic stroke and incorporated serum biomarkers related to inflammation, oxidative stress, and neuroplasticity. Participants demonstrated improvements in several upper-limb measurements, although significant differences between virtual reality and conventional occupational therapy were not consistent across all outcomes. This study illustrates the importance of combining clinical scales with biological and neurophysiological measures, while also demonstrating that promising mechanisms do not always translate into clear superiority over conventional therapy.

Robotic rehabilitation

Robot-assisted rehabilitation uses programmable devices to guide, assist, resist, or measure movement. Upper-limb systems include exoskeletons, end-effector robots, wearable gloves, and portable devices. Depending on the patient's abilities, robots may provide passive, active-assisted, active, or resisted training. Some systems detect the patient's voluntary effort and modify assistance in real time.

The principal advantage of robotic therapy is its capacity to deliver a large number of standardized and measurable repetitions. Robots can record variables such as movement trajectory, velocity, smoothness, accuracy, force, and range of motion. These data may help therapists monitor subtle changes that are not always detected through conventional clinical scales.

Nevertheless, completing a high number of repetitions is not sufficient by itself. If the robot provides excessive assistance, the patient may become a passive participant. This can reduce motor effort, attention, error processing, and sensory prediction, all of which are important for motor learning. Assistance should therefore be progressively reduced as the patient improves, following an "assist-as-needed" principle.

Systematic reviews generally report favorable but variable results. Bertani et al. (2017) found that robot-assisted therapy positively influenced upper-limb recovery. Veerbeek et al. (2017) identified improvements in motor control and strength, although the magnitude and clinical relevance of the effects differed across studies. Chien et al. (2020) concluded that robotic therapy may benefit patients during the subacute stage, but its superiority over equally intensive conventional therapy was not consistent.

These findings indicate that part of the benefit may arise from the additional treatment dose made possible by robotic devices. Consequently, studies comparing robot-assisted therapy plus usual care with usual care alone may overestimate the specific effect of the technology. Dose-matched comparisons are needed to determine whether robotics produces a therapeutic advantage beyond increasing repetition and treatment time.

Portable and wearable robots may improve access to rehabilitation outside specialized centers. Tseng et al. (2024) reported that portable upper-limb robotic systems showed potential benefits for motor function and activities of daily living. However, differences in device design, control mechanisms, intervention duration, and patient selection limit direct comparisons. Home-based use also requires safety protocols, remote supervision, technical support, and reliable methods for verifying adherence.

Integration of virtual reality and robotics

Virtual reality and robotics address different but complementary components of rehabilitation. Robotic devices provide physical interaction, assistance, resistance, and haptic information. Virtual reality provides meaningful goals, visual and auditory feedback, adjustable environments, and motivational elements. Their integration may produce a closed-loop system in which patient movement is measured continuously and task difficulty or robotic assistance is adjusted according to performance.

A network meta-analysis by Zhang et al. (2023) evaluated 61 randomized controlled trials involving 2,328 patients. The authors compared robot-assisted training, virtual reality, combined interventions, and conventional rehabilitation. Their findings suggested that robotic training combined with virtual reality may be advantageous for balance, while virtual reality may be particularly useful for improving daily function. However, these results should be interpreted

cautiously because the ranking of interventions was derived from studies with different devices, treatment doses, and participant characteristics.

The combined approach may be especially useful when robotic movement is linked to a meaningful virtual task. For example, a patient may use an assisted reaching movement to select objects in a simulated kitchen rather than repeatedly moving the arm without a functional context. This association can improve the relevance of training and may facilitate transfer to everyday activities. Nevertheless, functional transfer must be demonstrated using standardized measures and not assumed from performance within the technological system.

Current limitations and clinical implications

Several barriers prevent definitive conclusions about digital neurorehabilitation. The term “virtual reality” includes systems ranging from simple commercial games to fully immersive clinical platforms. Similarly, robotic therapy includes devices with substantially different mechanical structures, control algorithms, and therapeutic purposes. Combining all these interventions into a single category may conceal clinically meaningful differences.

Many studies also include small samples and short treatment periods. Participants with severe cognitive, visual, linguistic, or perceptual impairments are frequently excluded, even though these patients may have the greatest rehabilitation needs. Adverse effects such as cybersickness, dizziness, visual fatigue, musculoskeletal discomfort, frustration, and technology-related anxiety are not always evaluated consistently.

Clinical effectiveness should therefore be assessed through multiple domains: impairment, activity, participation, quality of life, safety, adherence, usability, and cost-effectiveness. Neuroimaging and biomarkers may help explain treatment mechanisms, but they should complement rather than replace functional evaluation. The ultimate purpose of digital neurorehabilitation is not to improve performance on a device; it is to increase independence and meaningful participation in daily life.

Current evidence supports virtual reality and robotics as complementary tools rather than universal replacements for conventional rehabilitation. Their effectiveness appears to depend on whether they increase active, intensive, task-specific, and progressively challenging practice. Patient selection, treatment dose, therapist supervision, and correspondence between digital exercises and real-world goals are essential. Future research must identify which patients benefit most, which technological characteristics produce meaningful effects, and whether these benefits persist after treatment concludes.

OBJETIVO GENERAL Y OBJETIVOS ESPECÍFICOS

General Objective

To critically analyze the effectiveness of virtual reality and robot-assisted rehabilitation in promoting neuroplasticity and improving motor function, functional independence, and participation in adults after stroke, considering the influence of treatment intensity, technological characteristics, recovery stage, and patient-related factors.

Specific Objectives

Cognitive Domain

1. **Identify** the neurobiological and motor-learning principles that explain the relationship between virtual reality, robotic rehabilitation, and experience-dependent neuroplasticity after stroke.
2. **Describe** the main characteristics, therapeutic applications, advantages, and limitations of virtual reality and robotic systems used in post-stroke neurorehabilitation.
3. **Compare** the effects of virtual reality, robot-assisted therapy, combined technological interventions, and conventional rehabilitation on motor function, balance, gait, dexterity, activities of daily living, and quality of life.
4. **Analyze** the influence of treatment dose, intervention duration, time since stroke, baseline impairment, feedback modality, level of immersion, and degree of robotic assistance on rehabilitation outcomes.

5. **Evaluate** the methodological quality and clinical relevance of systematic reviews, meta-analyses, randomized controlled trials, and neuroplasticity studies related to digital stroke rehabilitation.

Psychomotor Domain

6. **Organize** the extracted evidence using structured data-recording instruments that classify intervention characteristics, participant profiles, outcome measures, and principal findings.
7. **Construct** a comparative evidence framework that visually and systematically integrates virtual reality, robotic rehabilitation, conventional therapy, and combined interventions according to their mechanisms and reported outcomes.
8. **Apply** a reproducible literature-selection and evidence-synthesis procedure to examine studies relevant to digital neurorehabilitation after stroke.

Affective Domain

9. **Assess** the importance of patient motivation, treatment adherence, emotional response, perceived safety, and acceptance of technology in the effectiveness of digital neurorehabilitation.
10. **Value** the need for patient-centered, ethical, equitable, and accessible implementation of virtual reality and robotic systems, particularly for individuals with limited access to specialized rehabilitation services.
11. **Recognize** the importance of preserving therapist supervision, shared clinical decision-making, and individualized functional goals when incorporating digital technologies into rehabilitation.
12. **Formulate** evidence-based recommendations for integrating virtual reality and robotics as complementary tools within comprehensive post-stroke rehabilitation programs.

OBJETO DE ESTUDIO

The object of study is the use of virtual reality and robot-assisted rehabilitation as therapeutic strategies for promoting neuroplasticity and improving motor and functional recovery in adults who have experienced a stroke.

The phenomenon under investigation encompasses the interaction between digital rehabilitation technologies, experience-dependent neuroplasticity, and clinical recovery. The study focuses on how virtual environments, robotic assistance, task-specific practice, repetition, feedback, and progressive training may influence neural reorganization and translate into measurable improvements in movement and daily functioning.

Study Population

The population of interest consists of adults aged 18 years or older with a clinical diagnosis of ischemic or hemorrhagic stroke who present one or more neurological consequences requiring rehabilitation. These may include:

- Upper- or lower-limb motor impairment.
- Reduced strength, coordination, or manual dexterity.
- Gait and balance disorders.
- Spasticity or abnormal movement patterns.
- Limitations in activities of daily living.
- Reduced functional independence and social participation.

The study considers patients in the acute, subacute, and chronic stages of stroke recovery. This classification makes it possible to examine whether the timing of digital intervention influences clinical and neuroplastic outcomes.

Interventions Under Study

The interventions examined include:

1. **Virtual reality rehabilitation:** non-immersive, semi-immersive, and fully immersive systems used to train upper-limb function, gait, balance, coordination, postural control, and functional activities.
2. **Robot-assisted rehabilitation:** exoskeletons, end-effector robots, robotic gloves, portable devices, and other systems that provide passive, active-assisted, active, or resisted movement training.
3. **Combined interventions:** rehabilitation programs in which robotic assistance is integrated with virtual environments, gamified tasks, movement sensors, or computerized feedback.
4. **Comparison interventions:** conventional physical therapy, occupational therapy, usual care, no additional intervention, or dose-matched rehabilitation without virtual or robotic technology.

Main Variables

The principal independent variable is the use of virtual reality, robot-assisted rehabilitation, or a combination of both. Relevant intervention characteristics include treatment frequency, session duration, total treatment dose, level of immersion, type of robotic device, degree of assistance, feedback modality, task specificity, and level of patient participation.

The dependent variables include:

- Upper- and lower-limb motor function.
- Muscle strength and movement control.
- Manual dexterity and coordination.
- Balance, gait, and mobility.
- Spasticity.
- Performance of activities of daily living.
- Functional independence.
- Participation and quality of life.
- Treatment adherence and patient motivation.
- Cortical activation and functional connectivity.
- Neurophysiological and biological indicators of neuroplasticity.

Potential moderating variables include age, sex, stroke type, lesion location, neurological severity, time since stroke, baseline motor capacity, cognitive status, sensory impairment, comorbidities, rehabilitation intensity, and previous exposure to technology.

Unit of Analysis

The primary unit of analysis consists of peer-reviewed studies evaluating virtual reality or robot-assisted rehabilitation in adults after stroke. Priority is given to clinical guidelines, systematic reviews, meta-analyses, randomized controlled trials, and studies that assess neuroplasticity through neuroimaging, neurophysiological testing, or biological markers.

Each publication is analyzed according to:

- Study design and methodological quality.
- Participant characteristics and sample size.

- Stroke stage and severity.
- Type and characteristics of the intervention.
- Comparison group.
- Treatment frequency, intensity, and duration.
- Clinical and neurobiological outcome measures.
- Main findings and reported adverse effects.
- Follow-up duration.
- Limitations and potential sources of bias.

Delimitation of the Object of Study

The study is limited to adult post-stroke neurorehabilitation. It does not primarily examine rehabilitation for traumatic brain injury, spinal cord injury, cerebral palsy, multiple sclerosis, Parkinson's disease, or other neurological conditions. Studies involving these populations are considered only when they provide essential theoretical information about neuroplasticity or rehabilitation technology.

The review concentrates on motor and functional recovery. Cognitive, language, and emotional outcomes are included when they are directly associated with the analyzed interventions, but they do not constitute the central focus. Likewise, the study examines clinically oriented virtual reality and robotic systems rather than technologies designed exclusively for entertainment, diagnostic imaging, or non-rehabilitative purposes.

Operational Definition

For this study, **digital neurorehabilitation** is defined as the structured therapeutic use of interactive virtual environments, robotic devices, sensors, or computerized feedback systems to provide individualized, repetitive, measurable, and task-oriented training after stroke.

A digital intervention is considered potentially effective when it produces statistically and clinically relevant improvements in validated motor or functional outcomes without causing unacceptable adverse effects. Evidence of neuroplasticity is considered when studies report changes in cortical activation, neural connectivity, corticospinal excitability, functional brain organization, or biological markers associated with neural adaptation.

Therefore, the object of study is not limited to determining whether a technological device improves a clinical score. It also examines the mechanisms through which improvement may occur, the conditions under which benefits are most likely, and the extent to which gains transfer to independence and participation in daily life.

METODOLOGÍA

Study Design

This study was conducted as a structured integrative literature review based on the Scientific Method. This approach allowed the integration of clinical, technological, and neurobiological evidence concerning virtual reality, robot-assisted rehabilitation, and neuroplasticity after stroke.

The research process included identification of the problem, formulation of the research question and hypotheses, systematic collection of scientific evidence, critical assessment of the selected publications, comparative analysis of the findings, and formulation of evidence-based conclusions. The identification and selection of studies were organized according to the principles of the PRISMA 2020 statement.

A new meta-analysis was not performed because the included publications presented substantial heterogeneity in participant characteristics, stroke stage, technological devices, intervention duration, treatment intensity, comparison groups, and outcome measures. The findings were therefore examined through a structured qualitative and descriptive synthesis.

Research Question

The principal research question was:

To what extent do virtual reality and robot-assisted rehabilitation promote neuroplasticity and improve motor and functional outcomes in adults after stroke compared with conventional rehabilitation?

The question was structured using the PICO framework:

- **Population:** Adults with ischemic or hemorrhagic stroke.
- **Intervention:** Virtual reality, robot-assisted rehabilitation, or a combination of both technologies.
- **Comparison:** Conventional rehabilitation, usual care, no additional intervention, or dose-matched therapy.
- **Outcomes:** Neuroplasticity, motor function, dexterity, balance, gait, activities of daily living, functional independence, participation, and quality of life.

Sources of Information

Scientific evidence was identified through searches in the following databases and sources:

- PubMed/MEDLINE.
- Cochrane Library.
- Scopus.
- Web of Science.
- IEEE Xplore.
- PEDro.
- Official journal and publisher databases.

The reference lists of relevant systematic reviews, meta-analyses, randomized controlled trials, and clinical guidelines were also examined to identify additional publications directly related to the research question.

The final search update was established as August 11, 2026.

Search Strategy

The literature search combined controlled vocabulary and free-text terms related to four principal concepts:

1. Stroke and post-stroke recovery.
2. Virtual reality and virtual environments.
3. Robotic and technology-assisted rehabilitation.
4. Neuroplasticity, motor recovery, and functional independence.

The principal terms included stroke, post-stroke, cerebrovascular accident, virtual reality, immersive virtual reality, virtual environment, interactive video gaming, robotics, robot-assisted rehabilitation, rehabilitation robot, robotic

exoskeleton, robotic glove, neuronal plasticity, neuroplasticity, cortical reorganization, motor recovery, upper-limb function, gait, balance, activities of daily living, rehabilitation, and neurorehabilitation.

The terms were combined using Boolean operators such as **AND** and **OR**. The search syntax was adapted to the indexing system of each database while preserving the same conceptual structure.

No filter based on positive outcomes was applied. Publications reporting favorable, neutral, negative, or inconclusive findings were considered to reduce selective interpretation.

Eligibility Criteria

Inclusion Criteria

Publications were included when they met the following criteria:

1. The population consisted of adults aged 18 years or older.
2. Participants had a clinical diagnosis of ischemic or hemorrhagic stroke.
3. The intervention involved virtual reality, robot-assisted rehabilitation, or a combination of both technologies.
4. At least one motor, functional, neurophysiological, neuroimaging, or neuroplasticity-related outcome was reported.
5. The publication was a clinical guideline, systematic review, meta-analysis, randomized controlled trial, controlled clinical study, or relevant neuroplasticity study.
6. The study was published in a peer-reviewed scientific journal.
7. The publication was available in English or Spanish.
8. The study was published between January 2005 and August 2026.
9. The bibliographic information and DOI or another verifiable identifier were available.

Foundational publications on motor learning and post-stroke neuroplasticity were also included when they provided essential theoretical information, even if they did not directly evaluate virtual reality or robotic devices.

Exclusion Criteria

Publications were excluded when:

1. The principal population consisted of children or adolescents.
2. The intervention addressed another neurological condition without presenting separate results for stroke survivors.
3. The technology was used exclusively for diagnosis, assessment, or entertainment and did not include a therapeutic component.
4. The publication was an editorial, opinion article, commercial document, conference abstract without sufficient data, or non-peer-reviewed report.
5. No relevant motor, functional, neuroplasticity, safety, adherence, or quality-of-life outcome was reported.
6. The complete text or sufficient methodological information was unavailable.
7. The publication duplicated data already presented in another selected study. In these cases, the most complete or updated report was retained.

Study Selection

All identified publications were organized in a reference-management system. Duplicate records were detected using the title, authors, publication year, DOI, and journal information.

Study selection was conducted in three stages:

1. **Title review:** Publications clearly unrelated to stroke rehabilitation, virtual reality, robotics, or neuroplasticity were excluded.
2. **Abstract review:** Potentially relevant studies were assessed according to their population, intervention, comparison, outcomes, and methodological design.
3. **Full-text review:** The complete publications were examined to verify compliance with all eligibility criteria.

The reason for excluding each full-text publication was recorded using predefined categories, including inappropriate population, unrelated intervention, absence of relevant outcomes, insufficient methodological information, duplicate data, and non-peer-reviewed publication.

The selection process was organized for presentation through a PRISMA flow diagram.

Data Extraction

Information from each eligible publication was recorded in a standardized data-extraction matrix. The following variables were collected:

- Author and year of publication.
- Country of origin.
- Study design.
- Sample size.
- Participant age and sex.
- Type and stage of stroke.
- Baseline neurological impairment.
- Type of virtual reality or robotic system.
- Level of virtual reality immersion.
- Type and degree of robotic assistance.
- Session frequency and duration.
- Total intervention period.
- Characteristics of the comparison group.
- Clinical outcome instruments.
- Motor and functional results.
- Neuroimaging, neurophysiological, or biological findings.
- Adverse events.
- Treatment adherence and acceptability.

- Follow-up duration.
- Main conclusions.
- Methodological limitations.

Information that was not reported in the original publication was classified as “not specified.” Missing values were not estimated or inferred.

Methodological Quality Assessment

The methodological quality of each publication was evaluated using an instrument appropriate to its design:

- **AMSTAR 2** for systematic reviews and meta-analyses.
- **Cochrane Risk of Bias 2** for randomized controlled trials.
- **AGREE II** for clinical practice guidelines.
- **ROBINS-I** for non-randomized intervention studies.
- **SANRA** for narrative reviews used as theoretical support.

The evaluation considered randomization, allocation concealment, blinding, baseline comparability, incomplete outcome data, selective reporting, intervention fidelity, sample size, follow-up duration, and conflicts of interest.

Publications were not automatically excluded because of moderate methodological limitations. Instead, studies with stronger methodology and more consistent findings received greater interpretive weight.

Evidence Synthesis

The selected evidence was organized into four principal categories:

1. Neuroplasticity and motor-learning mechanisms after stroke.
2. Virtual reality rehabilitation.
3. Robot-assisted rehabilitation.
4. Combined virtual reality and robotic interventions.

Studies were compared according to stroke stage, baseline impairment, intervention characteristics, treatment dose, outcome measures, methodological quality, and follow-up duration.

The direction of findings was classified as:

- Predominantly favorable.
- Conditional or mixed.
- Equivalent to conventional rehabilitation.
- Inconclusive.
- Unfavorable or associated with adverse effects.

Statistical significance was differentiated from clinical relevance. When available, effect sizes, confidence intervals, minimal clinically important differences, and long-term outcomes were considered.

Special attention was given to the intensity of the comparison therapy. Studies comparing technological rehabilitation plus usual care with usual care alone were distinguished from studies comparing digital rehabilitation with an equivalent dose of conventional therapy.

Reliability and Reproducibility

To facilitate replication, the research process maintained a methodological record containing:

- Databases consulted.
- Search dates.
- Search terms and combinations.
- Inclusion and exclusion criteria.
- Duplicate-removal procedure.
- Eligibility forms.
- Reasons for full-text exclusion.
- Data-extraction matrix.
- Quality-assessment instruments.
- Final list of included publications.

The selection criteria, variables, and analytical categories were defined before the final synthesis. Any methodological modification was documented and justified.

Ethical Considerations

The study analyzed previously published scientific literature and did not involve direct participation of patients, collection of biological samples, or access to identifiable personal information. Therefore, informed consent and direct approval for human experimentation were not required.

Ethical standards were maintained by accurately representing the original findings, including neutral and negative results, acknowledging methodological limitations, avoiding fabrication or alteration of data, and properly citing the original sources.

The review also considered patient safety, autonomy, data privacy, accessibility, and equitable access to digital rehabilitation technologies.

FASES DEL DESARROLLO

Phase 1. Identification and Delimitation of the Problem

The first phase consisted of identifying the clinical and scientific problem: many stroke survivors continue to experience motor and functional limitations despite completing conventional rehabilitation programs. Although virtual reality and robot-assisted therapy have shown promising results, uncertainty remains regarding their real clinical effectiveness, their capacity to induce adaptive neuroplasticity, and the conditions under which they provide benefits beyond conventional treatment.

The problem was delimited to adult patients with ischemic or hemorrhagic stroke who received virtual reality, robotic rehabilitation, or a combination of both. The analysis focused on motor recovery, balance, gait, dexterity, activities of daily living, functional independence, quality of life, and indicators of neuroplasticity.

The product of this phase was a clearly defined research problem and object of study.

Phase 2. Formulation of the Research Question and Hypotheses

The research question was structured using the PICO framework:

- **Population:** Adults after ischemic or hemorrhagic stroke.
- **Intervention:** Virtual reality, robotic rehabilitation, or combined technological therapy.
- **Comparison:** Conventional rehabilitation, usual care, no additional treatment, or dose-matched therapy.
- **Outcomes:** Motor, functional, neurophysiological, and neuroplasticity-related outcomes.

The principal question was formulated as follows:

To what extent do virtual reality and robot-assisted rehabilitation promote neuroplasticity and improve motor and functional outcomes in adults after stroke compared with conventional rehabilitation?

The principal hypothesis proposed that these technologies would produce greater benefits when they delivered intensive, repetitive, task-specific, progressively challenging, and feedback-rich training. It was also proposed that effectiveness would vary according to stroke stage, baseline impairment, treatment dose, active participation, and technological characteristics.

The product of this phase was a set of research questions and hypotheses aligned with the general and specific objectives.

Phase 3. Design of the Review Protocol

Before the final evidence synthesis, a review protocol was established to reduce arbitrary decisions. This protocol specified:

- Databases and information sources.
- Search terms and Boolean operators.
- Publication period.
- Inclusion and exclusion criteria.
- Screening procedure.
- Variables to be extracted.
- Methodological quality instruments.
- Evidence-synthesis strategy.

The review was structured according to PRISMA 2020 principles. A standardized eligibility form and data-extraction matrix were prepared. The protocol also established that neutral and negative findings would be considered alongside positive findings to reduce selective interpretation.

The product of this phase was a reproducible methodological protocol.

Phase 4. Systematic Search and Identification of Evidence

A structured search was conducted in PubMed/MEDLINE, Cochrane Library, Scopus, Web of Science, IEEE Xplore, PEDro, and official journal databases. Controlled vocabulary and free-text terms related to stroke, virtual reality, robotics, rehabilitation, motor recovery, and neuroplasticity were combined using Boolean operators.

The search syntax was adapted to each database without changing the conceptual structure. Reference lists from relevant guidelines, systematic reviews, and meta-analyses were also examined to identify additional publications.

For each database, the following information was documented:

- Name of the database.
- Date of the search.
- Complete search equation.
- Filters applied.
- Number of records obtained.

The product of this phase was the initial database of potentially relevant scientific publications.

Phase 5. Screening and Selection of Studies

The records were reviewed through a sequential selection procedure. First, duplicate publications were identified using the DOI, title, authorship, and year. The remaining records were screened by title and abstract.

Studies that appeared to meet the eligibility criteria were evaluated in full text. At this stage, the population, intervention, outcomes, study design, and availability of sufficient methodological information were verified.

Reasons for exclusion were recorded using predefined categories, including:

- Incorrect population.
- Unrelated intervention.
- Absence of relevant outcomes.
- Non-therapeutic use of technology.
- Insufficient methodological information.
- Duplicate data.
- Non-peer-reviewed publication.

The study-selection process was organized for presentation in a PRISMA flow diagram. The product of this phase was the final group of eligible studies.

Phase 6. Data Extraction and Quality Assessment

A standardized matrix was used to extract comparable information from each publication. The matrix included participant characteristics, stroke stage, intervention type, treatment intensity, session duration, comparison group, outcome measures, follow-up, main findings, adverse effects, and study limitations.

Data not reported in the original publication were classified as “not specified.” No missing values were estimated without a valid statistical or methodological basis.

Methodological quality was evaluated according to study design:

- AMSTAR 2 for systematic reviews and meta-analyses.
- Cochrane RoB 2 for randomized trials.
- AGREE II for clinical guidelines.

- ROBINS-I for non-randomized intervention studies.
- SANRA for narrative reviews used as theoretical support.

This phase also examined conflicts of interest, sample size, comparability between groups, attrition, selective reporting, intervention fidelity, and follow-up duration.

The product of this phase was a critically evaluated evidence matrix.

Phase 7. Comparative Analysis and Evidence Synthesis

The selected studies were organized into four categories:

1. Neuroplasticity and motor-learning mechanisms.
2. Virtual reality rehabilitation.
3. Robot-assisted rehabilitation.
4. Combined virtual reality and robotic interventions.

Within each category, studies were compared according to stroke stage, baseline impairment, technological characteristics, treatment dose, outcome instruments, and methodological quality.

The analysis distinguished between:

- Statistical and clinical significance.
- Improvement in impairment and improvement in daily function.
- Technology-specific effects and benefits caused by additional therapy time.
- Short-term gains and persistent outcomes.
- Neural changes associated with restitution and those related to compensation.

Findings were classified as favorable, equivalent, partially favorable, inconclusive, or unfavorable. Greater interpretive weight was assigned to high-quality systematic reviews, meta-analyses, clinical guidelines, and randomized controlled trials.

Because the interventions and measurements were heterogeneous, a structured qualitative synthesis was selected instead of combining all results in a new meta-analysis. The product of this phase was an integrated interpretation of the clinical and neurobiological evidence.

Phase 8. Interpretation, Conclusions, and Recommendations

The synthesized evidence was interpreted in relation to the research question, hypotheses, and objectives. This phase examined whether the available findings supported the proposed relationship between digital training, neuroplasticity, and functional recovery.

Conclusions were formulated only when supported by consistent and methodologically reliable evidence. In areas where the findings differed, the uncertainty and possible reasons for disagreement were explicitly reported.

Recommendations were developed regarding:

- Integration with conventional therapy.
- Individualized treatment selection.
- Appropriate robotic assistance.

- Virtual reality immersion and feedback.
- Functional transfer to daily activities.
- Patient safety and acceptability.
- Future clinical trials and implementation studies.

RESULTADOS Y DISCUSIÓN

Figure 1.

Thematic distribution of the publications included in the review

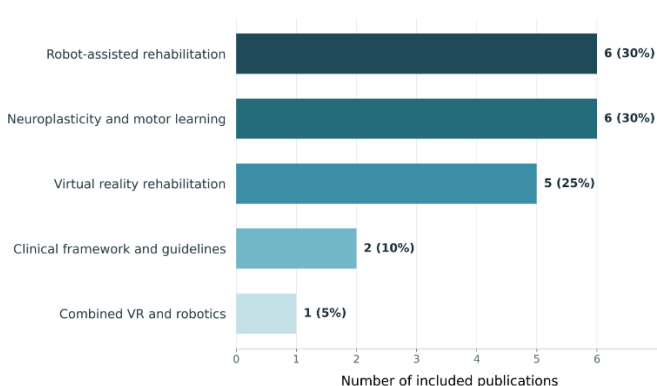


Figure 1 presents the thematic distribution of the 20 publications included in the structured review. Each publication was assigned to one principal category according to its predominant research objective. Categories were considered mutually exclusive; therefore, each publication was counted only once even when it addressed more than one component of digital neurorehabilitation. The percentages consequently represent the composition of the selected evidence base and not the prevalence, effectiveness, or superiority of the interventions.

Robot-assisted rehabilitation was represented by six publications, corresponding to 30% of the evidence. This category included systematic reviews and meta-analyses examining robotic therapy for upper-limb recovery, activities of daily living, motor control, muscle strength, treatment portability, and intervention dose. The selected publications evaluated several types of robotic technology, including exoskeletons, end-effector systems, wearable devices, and portable robots.

The six publications assigned to this category were those by Bertani et al. (2017), Chien et al. (2020), Mehrholz et al. (2020), Tseng et al. (2024), Veerbeek et al. (2017), and Zhang et al. (2022). Collectively, these sources represent a substantial component of the review because robotic upper-limb rehabilitation has been evaluated through multiple evidence-synthesis designs. The available literature includes conventional pairwise meta-analyses and network meta-analysis, permitting comparisons among robotic devices, conventional therapy, and different treatment configurations (Bertani et al., 2017; Chien et al., 2020; Mehrholz et al., 2020).

Portable robotic systems were included within this category because they retain the defining characteristics of robot-assisted rehabilitation while introducing a different delivery model. The review by Tseng et al. (2024), for example, specifically evaluated portable upper-limb robots. The presence of this publication allows the evidence base to include both facility-based robotic rehabilitation and more compact systems potentially applicable to decentralized training (Tseng et al., 2024).

The second largest category was neuroplasticity and motor learning, also represented by six publications or 30% of the total. These studies provide the theoretical and neurobiological foundation necessary to analyze the mechanisms through which digital rehabilitation may influence recovery. They address cortical reorganization, interhemispheric interactions, motor learning, experience-dependent plasticity, brain-derived neurotrophic factor, adaptive and maladaptive responses, and the biological conditions that influence post-stroke recovery.

This category included Dimyan and Cohen (2011), Di Pino et al. (2014), Krakauer et al. (2012), Li (2017), Mang et al. (2013), and Takeuchi and Izumi (2013). These publications do not all evaluate a specific digital device; instead, they establish the mechanisms and therapeutic principles against which virtual and robotic interventions can be examined. Their inclusion makes it possible to differentiate an improvement in clinical performance from evidence suggesting a change in neural organization (Dimyan & Cohen, 2011; Di Pino et al., 2014).

The equal representation of robotic rehabilitation and neuroplasticity—six publications each—shows that the review was constructed around both clinical intervention evidence and biological plausibility. The robotic publications contribute data on functional outcomes, whereas the neuroplasticity publications provide concepts for evaluating whether repetitive, task-specific, active, and feedback-rich training is consistent with established principles of post-stroke motor recovery. This balance is descriptive of the selected literature and should not be interpreted as evidence that both areas have an equivalent total volume of research.

Virtual reality rehabilitation comprised five publications, representing 25% of the evidence base. This group included research on non-immersive and immersive interventions, upper-limb rehabilitation, locomotor recovery, cortical activation, biological markers, and functional outcomes. The category contained one updated Cochrane review, systematic reviews and meta-analyses, and clinical studies examining potential neural mechanisms.

The five publications were those by Hao et al. (2022), Huang et al. (2022), Laver et al. (2025), Soleimani et al. (2024), and You et al. (2005). Hao et al. concentrated on neural plasticity associated with virtual reality, whereas Huang et al. evaluated motor outcomes alongside biomarkers related to inflammation, oxidative stress, and neuroplasticity. You et al. provided early randomized evidence relating virtual reality to cortical reorganization and locomotor recovery (Hao et al., 2022; Huang et al., 2022; You et al., 2005).

The systematic reviews by Soleimani et al. (2024) and Laver et al. (2025) provided broader evaluations of clinical effectiveness. Soleimani et al. included 55 studies and 2,142 participants in their analysis of upper-limb rehabilitation. The updated Cochrane review offered an additional high-level synthesis of virtual reality interventions across post-stroke rehabilitation outcomes. These publications were classified under virtual reality because that technology constituted their central intervention, even when the studies also evaluated motor learning or neuroplasticity (Soleimani et al., 2024; Laver et al., 2025).

Two publications, equivalent to 10% of the selected evidence, were classified as clinical framework and rehabilitation guidelines. This category included the general stroke-rehabilitation review by Langhorne et al. (2011) and the American Heart Association/American Stroke Association guideline developed by Winstein et al. (2016). These sources establish the clinical standards against which digital interventions are compared, including multidisciplinary care, functional assessment, task-specific practice, treatment intensity, and patient-centered rehabilitation (Langhorne et al., 2011; Winstein et al., 2016).

Only one publication, representing 5% of the evidence, was assigned specifically to combined virtual reality and robotic rehabilitation. Zhang et al. (2023) conducted a systematic review and network meta-analysis comparing robot-assisted training, virtual reality, combined interventions, and conventional rehabilitation. The analysis included 61 randomized controlled trials and 2,328 patients. It was retained as a separate category because its principal objective was the comparative evaluation of the technologies individually and in combination, rather than the isolated assessment of only one intervention (Zhang et al., 2023).

The small proportion of publications in the combined category should be interpreted strictly as a characteristic of the 20-source sample. It does not demonstrate that combined interventions are ineffective. It indicates that fewer of the selected high-quality publications directly evaluated integrated virtual reality and robotics as a distinct therapeutic strategy.

Overall, 12 of the 20 publications, equivalent to 60%, primarily examined a specific digital intervention: six focused on robotics, five on virtual reality, and one on their combination. The remaining eight publications, equivalent to 40%, provided neurobiological, motor-learning, clinical, or guideline-based foundations. Thus, the selected evidence base contains a greater proportion of intervention-focused publications while preserving a substantial theoretical and clinical framework for interpreting the reported outcomes.

Figure 2.

Distribution of the included publications according to study design

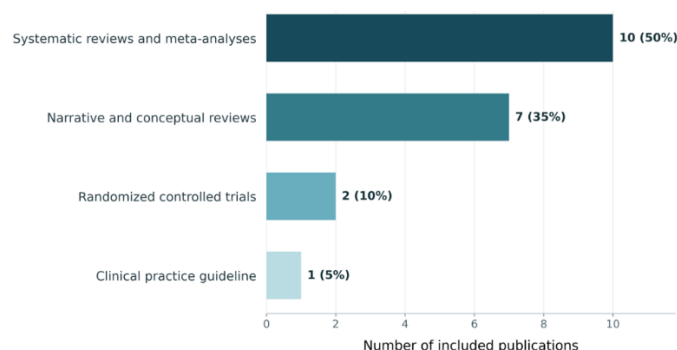


Figure 2 presents the distribution of the 20 included publications according to their principal methodological design. Each publication was classified only once, based on the design used to generate its main findings. The categories included systematic reviews and meta-analyses, narrative or conceptual reviews, randomized controlled trials, and clinical practice guidelines. The percentages describe the methodological composition of the evidence selected for this article and should not be interpreted as direct measurements of intervention effectiveness.

Systematic reviews and meta-analyses represented the largest category, with 10 publications, equivalent to 50% of the total evidence base. This group included five publications primarily focused on robotic rehabilitation, three on virtual reality, one on the combination of robotics and virtual reality, and one on the duration and functional effects of robot-assisted therapy.

The robotic evidence syntheses included the studies by Bertani et al. (2017), Chien et al. (2020), Mehrholz et al. (2020), Tseng et al. (2024), and Veerbeek et al. (2017). These publications analyzed clinical outcomes such as upper-limb motor control, muscle strength, activities of daily living, treatment intensity, device portability, and differences between robotic and conventional rehabilitation. The network meta-analysis by Mehrholz et al. also allowed comparisons among different robotic-training approaches rather than limiting the analysis to one intervention-versus-control comparison (Bertani et al., 2017; Chien et al., 2020; Mehrholz et al., 2020).

The systematic reviews focused on virtual reality were those by Hao et al. (2022), Laver et al. (2025), and Soleimani et al. (2024). Hao et al. examined neuroplastic changes associated with virtual reality, including cortical activation and functional connectivity. Soleimani et al. synthesized the results of 55 studies involving 2,142 participants, while the updated Cochrane review by Laver et al. provided a broader evaluation of virtual reality across different post-stroke rehabilitation outcomes (Hao et al., 2022; Laver et al., 2025; Soleimani et al., 2024).

The combined-intervention group was represented by the network meta-analysis of Zhang et al. (2023), which included 61 randomized controlled trials and 2,328 patients. This study compared robot-assisted therapy, virtual reality, combined interventions, and conventional rehabilitation across balance, gait, and daily-function outcomes. Zhang et al. (2022) contributed an additional meta-analysis focused on the short- and long-term effects of robot-assisted therapy on upper-limb function and activities of daily living (Zhang et al., 2023; Zhang et al., 2022).

The predominance of evidence syntheses means that a considerable proportion of the selected literature summarized multiple primary studies and patient samples. However, the 50% value should not be used to calculate a combined

number of participants because some reviews may include overlapping primary trials. Adding the sample sizes reported by all reviews would therefore risk counting the same participants more than once.

Narrative and conceptual reviews constituted the second-largest category, with seven publications or 35% of the evidence base. These publications were included primarily to explain the neurobiological and clinical foundations of stroke recovery rather than to provide pooled estimates of intervention effectiveness.

Dimyan and Cohen (2011) examined neuroplasticity in the context of motor rehabilitation, while Di Pino et al. (2014) proposed a model of brain-plasticity modulation relevant to neurorehabilitation. Krakauer et al. (2012) analyzed principles derived from animal models, and Takeuchi and Izumi (2013) reviewed post-stroke motor recovery with an emphasis on neural plasticity. Together, these sources described mechanisms such as cortical reorganization, changes in excitability, recruitment of surviving networks, and experience-dependent motor learning (Dimyan & Cohen, 2011; Di Pino et al., 2014; Krakauer et al., 2012; Takeuchi & Izumi, 2013).

Li (2017) examined the relationship among spasticity, motor recovery, and neural plasticity, whereas Mang et al. (2013) explored the influence of aerobic exercise, genetic variation, and brain-derived neurotrophic factor on rehabilitation-induced plasticity. Langhorne et al. (2011) provided a broader clinical review of stroke rehabilitation, including treatment organization and established rehabilitation principles (Li, 2017; Mang et al., 2013; Langhorne et al., 2011).

These narrative and conceptual publications represent 35% of the selected evidence because the article examines not only whether digital interventions produce functional changes, but also whether the reported outcomes are consistent with recognized mechanisms of neuroplasticity. Their findings are theoretical or interpretive and are therefore not treated as equivalent to pooled estimates from meta-analyses or direct measurements from clinical trials.

Randomized controlled trials accounted for two publications, equivalent to 10% of the evidence. The first was the study by You et al. (2005), which examined virtual reality–induced cortical reorganization and locomotor recovery in chronic stroke. This publication provided direct experimental evidence connecting a virtual reality intervention with both functional and cerebral outcomes (You et al., 2005).

The second randomized controlled trial was conducted by Huang et al. (2022) and included 30 patients with chronic stroke. It compared immersive virtual reality motor training with conventional occupational therapy and incorporated clinical measurements alongside serum biomarkers related to inflammation, oxidative stress, and neuroplasticity. The study reported improvements over time in several clinical variables, although between-group differences were not consistent across every clinical and biological outcome (Huang et al., 2022).

The relatively small number of individual randomized trials in this review does not mean that the broader evidence base contains only two trials. Multiple randomized studies were already incorporated within the included systematic reviews and meta-analyses. These two publications were retained separately because they directly measured neuroplasticity-related outcomes and were particularly relevant to the central research question.

One publication, corresponding to 5% of the evidence, was classified as a clinical practice guideline. The guideline by Winstein et al. (2016), developed for the American Heart Association/American Stroke Association, provided recommendations for adult stroke rehabilitation and recovery. It established the clinical framework for evaluating treatment intensity, task-specific practice, multidisciplinary care, functional assessment, and integration of rehabilitation interventions (Winstein et al., 2016).

Overall, 11 of the 20 publications—55%—represented high-level evidence syntheses or clinical guidance: 10 systematic reviews or meta-analyses and one guideline. Nine publications—45%—provided conceptual analysis or direct experimental evidence. This distribution allowed the results to integrate pooled clinical findings with mechanistic explanations and selected primary measurements.

Figure 3.

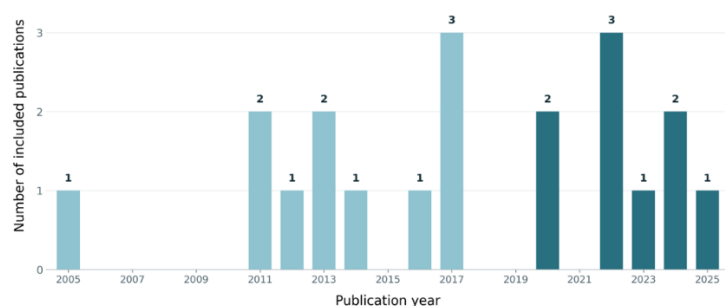
Chronological distribution of the publications included in the review, 2005–2025

Figure 3 presents the chronological distribution of the 20 publications selected for the review. The horizontal axis covers the period from 2005 to 2025, including years in which no selected publication was identified. The vertical axis represents the number of included publications corresponding to each year.

The graph describes the temporal composition of the selected evidence and not the total annual scientific production on digital neurorehabilitation. Years without a bar indicate only that none of the 20 selected sources was published during that year; they do not demonstrate an absence of research activity.

The earliest publication included in the review was published in 2005. You et al. (2005) conducted an experimenter-blinded randomized study evaluating virtual reality–induced cortical reorganization and locomotor recovery in patients with chronic stroke. This study was retained because it directly connected a virtual rehabilitation intervention with both functional recovery and changes in cerebral activation (You et al., 2005).

No selected publications corresponded to the period from 2006 through 2010. The chronological sequence resumed in 2011 with two publications. Dimyan and Cohen (2011) reviewed neuroplasticity in motor rehabilitation after stroke, whereas Langhorne et al. (2011) provided a broader clinical review of stroke rehabilitation. These publications established complementary foundations: one focused on neural reorganization and the other on the clinical organization and principles of rehabilitation (Dimyan & Cohen, 2011; Langhorne et al., 2011).

One publication was included from 2012. Krakauer et al. (2012) examined how evidence from animal models could inform neurorehabilitation, emphasizing the importance of distinguishing spontaneous recovery, compensation, and rehabilitation-induced restitution. The publication provided theoretical support for evaluating whether technology-assisted treatment follows established principles of motor learning (Krakauer et al., 2012).

Two publications were included from 2013. Mang et al. (2013) analyzed the relationship among rehabilitation, aerobic exercise, genetic variation, and brain-derived neurotrophic factor. Takeuchi and Izumi (2013) reviewed post-stroke motor recovery with an emphasis on neural plasticity. Both publications contributed mechanistic evidence rather than direct comparisons of digital devices (Mang et al., 2013; Takeuchi & Izumi, 2013).

The single publication from 2014 was the review by Di Pino et al. (2014), which presented a model for understanding and modulating brain plasticity after stroke. This study addressed cortical excitability and interhemispheric interactions relevant to the interpretation of rehabilitation-induced neural changes (Di Pino et al., 2014).

One publication was identified from 2016: the American Heart Association/American Stroke Association guideline developed by Winstein et al. (2016). This guideline provided a clinical framework for adult stroke rehabilitation, including treatment organization, functional assessment, intensity, task-specific practice, and professional supervision (Winstein et al., 2016).

The first maximum in the temporal distribution occurred in 2017, with three publications. These included two systematic reviews and meta-analyses of robot-assisted upper-limb rehabilitation and one review addressing spasticity, motor recovery, and neural plasticity.

Bertani et al. (2017) and Veerbeek et al. (2017) synthesized evidence on robotic upper-limb therapy. Their analyses examined motor function, muscle strength, and related clinical outcomes, although differences in device design, comparison interventions, and treatment doses contributed to heterogeneous findings. Li (2017) provided the neuroplasticity component by analyzing the relationship between post-stroke spasticity and motor recovery (Bertani et al., 2017; Veerbeek et al., 2017; Li, 2017).

No selected publications corresponded to 2018 or 2019. In 2020, two systematic reviews were included. Chien et al. (2020) examined robot-assisted therapy during the subacute stage of stroke, while Mehrholz et al. (2020) used network meta-analysis to compare robotic-assisted arm-training approaches for upper-limb function and activities of daily living. Both publications expanded the evidence related to comparative robotic effectiveness (Chien et al., 2020; Mehrholz et al., 2020).

No selected publication was assigned to 2021. The second maximum occurred in 2022, when three publications were included. Unlike the 2017 concentration, the 2022 group covered both virtual reality and robotics.

Hao et al. (2022) systematically reviewed changes in neural plasticity associated with virtual reality. Huang et al. (2022) conducted a randomized controlled trial incorporating clinical outcomes and serum biomarkers, while Zhang et al. (2022) evaluated the short- and long-term effects of robot-assisted therapy through a meta-analysis of randomized trials (Hao et al., 2022; Huang et al., 2022; Zhang et al., 2022).

One publication was included from 2023. Zhang et al. (2023) performed a systematic review and network meta-analysis comparing robot-assisted training, virtual reality, combined interventions, and conventional therapy. The study included 61 randomized controlled trials and 2,328 participants and evaluated balance, gait, and daily functioning (Zhang et al., 2023).

Two publications corresponded to 2024. Soleimani et al. (2024) published a systematic review and meta-analysis of virtual reality for upper-limb rehabilitation, including 55 studies and 2,142 patients. Tseng et al. (2024) evaluated portable upper-limb rehabilitation robots, adding a focus on wearable and transportable technological systems (Soleimani et al., 2024; Tseng et al., 2024).

The most recent publication included in the review was the 2025 update of the Cochrane review on virtual reality for stroke rehabilitation. It represents the latest high-level evidence synthesis incorporated into the study and updates the assessment of virtual reality across different rehabilitation outcomes (Laver et al., 2025).

When the publications were grouped into broader periods, seven sources—35%—were published between 2005 and 2014. Four publications—20%—corresponded to 2015–2019. Nine publications—45%—were published between 2020 and 2025. Therefore, almost half of the selected evidence was produced during the most recent six-year period represented in the review.

The chronological pattern also shows a change in the type of evidence included. Earlier publications predominantly established neuroplasticity, motor-learning, and general rehabilitation concepts. From 2017 onward, systematic reviews and meta-analyses of robotic and virtual reality interventions became more prominent. The most recent period incorporated network meta-analysis, biomarker evaluation, portable robotic devices, immersion-related analyses, and an updated Cochrane review.

Figure 4.

Participant samples reported in selected quantitative evidence syntheses

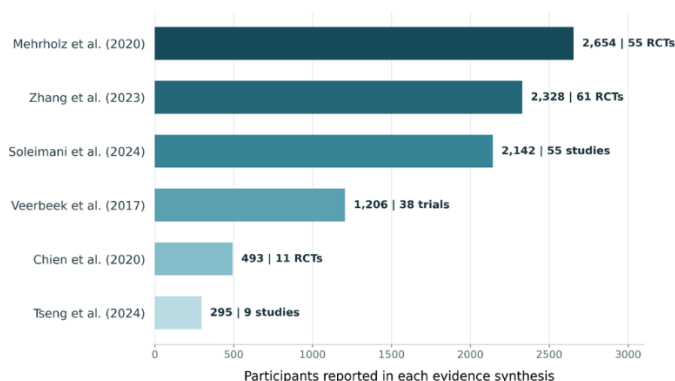


Figure 4 compares the number of participants and studies reported in six systematic reviews or meta-analyses included in the article. These publications were selected for the figure because their abstracts or full reports provided a clearly verifiable total number of studies and participants.

The graph includes three evidence syntheses focused on robot-assisted rehabilitation, one focused on portable robots, one on virtual reality, and one comparing virtual reality, robotics, combined interventions, and conventional rehabilitation. The reported samples ranged from 295 to 2,654 participants. The median sample size across the six publications was 1,674 participants.

These sample sizes must be interpreted independently. They cannot be added to calculate a total number of unique patients because different systematic reviews may include the same randomized controlled trials. Such overlap is particularly likely among publications addressing robot-assisted upper-limb rehabilitation.

The largest reported sample corresponded to Mehrholz et al. (2020), whose network meta-analysis included 55 randomized controlled trials and 2,654 stroke survivors. The study evaluated electromechanical and robot-assisted arm-training approaches, using activities of daily living, upper-limb function, arm strength, and safety as principal outcomes.

Although Mehrholz et al. analyzed the largest participant sample shown in the figure, the authors found that none of the robotic intervention categories produced statistically significant improvements after the heterogeneity of the studies was considered. This result refers to the comparisons and analytical framework used in that network meta-analysis and does not indicate that individual participants failed to improve (Mehrholz et al., 2020).

The second-largest sample was reported by Zhang et al. (2023). Their systematic review and network meta-analysis included 61 randomized controlled trials and 2,328 participants. It contained the largest number of trials among the six publications, although its participant sample was smaller than that of Mehrholz et al.

Zhang et al. compared robot-assisted training, virtual reality, combined robot-assisted and virtual reality interventions, and conventional therapy. Outcomes included balance, gait, and daily function. The review reported that the combined intervention occupied the highest ranking for balance, while virtual reality showed a favorable ranking for daily function. The number of trials provided a broad comparison network, but individual treatment comparisons were based on different subsets of the complete sample (Zhang et al., 2023).

Soleimani et al. (2024) reported the third-largest sample: 55 studies and 2,142 participants. Unlike the two preceding publications, this review focused specifically on virtual reality for upper-limb rehabilitation. It evaluated different levels of immersion and outcomes such as motor function, manual dexterity, functional independence, spasticity, and quality of life.

The review reported favorable results for several upper-limb and functional domains. It also identified differences related to immersion level, treatment duration, and time since stroke. Nevertheless, not every included study assessed the same outcome, and the complete sample of 2,142 participants was not necessarily available for every individual meta-analysis (Soleimani et al., 2024).

Veerbeek et al. (2017) included 38 trials and 1,206 participants. This review evaluated robot-assisted therapy for the paretic upper limb and reported small statistically significant improvements in motor control and muscle strength. The approximate improvement in motor control was around two points on the upper-extremity Fugl-Meyer Assessment.

The review did not identify corresponding effects for upper-limb capacity or basic activities of daily living. Thus, its reported sample supported analyses across different outcome levels, but the direction of the results was not identical for impairment-based and activity-based measurements (Veerbeek et al., 2017).

Chien et al. (2020) analyzed 11 randomized controlled trials involving 493 participants with subacute stroke. This review had a more restricted population than the larger robotic syntheses because it specifically examined patients during the subacute stage.

The included evidence was rated as low to moderate in quality. The results indicated that robot-assisted therapy produced outcomes similar to usual care for several variables, although selected benefits were reported. Because the study concentrated on the subacute period, its sample should not be directly equated with reviews that combined acute, subacute, and chronic populations (Chien et al., 2020).

The smallest evidence synthesis shown in Figure 4 was that of Tseng et al. (2024), with nine studies and 295 participants. Eight of the nine studies were included in the quantitative meta-analysis. The review specifically examined portable upper-limb rehabilitation robots, representing a narrower technological category than general robotic rehabilitation.

The authors reported a standardized mean difference of 0.696 for the Fugl-Meyer Assessment, with a reported confidence interval from 0.099 to 1.293 and statistical significance below 0.05. The review also described portable robotics and conventional rehabilitation as broadly comparable, despite favorable findings in some included studies. The smaller evidence base reflects the specific focus on portable devices rather than all robot-assisted systems (Tseng et al., 2024).

Across the six syntheses, the crude ratio of participants to included studies ranged from approximately 32 to 48 participants per study:

- * Mehrholz et al.: approximately 48 participants per trial.
- * Zhang et al.: approximately 38 participants per trial.
- * Soleimani et al.: approximately 39 participants per study.
- * Veerbeek et al.: approximately 32 participants per trial.
- * Chien et al.: approximately 45 participants per trial.
- * Tseng et al.: approximately 33 participants per study.

These ratios are descriptive and do not represent the actual sample size of every primary study because participant distribution was not uniform. Nevertheless, they show that the relatively large pooled samples were constructed from numerous studies that were generally small when considered individually.

The two largest robotic or comparative syntheses—Mehrholz et al. and Zhang et al.—included more than 2,300 participants each. The principal virtual reality synthesis shown in the figure—Soleimani et al.—included more than 2,100 participants. Consequently, both technological fields were represented by quantitative evidence involving thousands of observations, although the analyses addressed different populations, interventions, and outcomes.

The figure also demonstrates that the number of trials does not correspond perfectly to the total number of participants. Zhang et al. included more trials than Mehrholz et al. but fewer participants. This difference indicates variation in the average size of the primary studies included in each review.

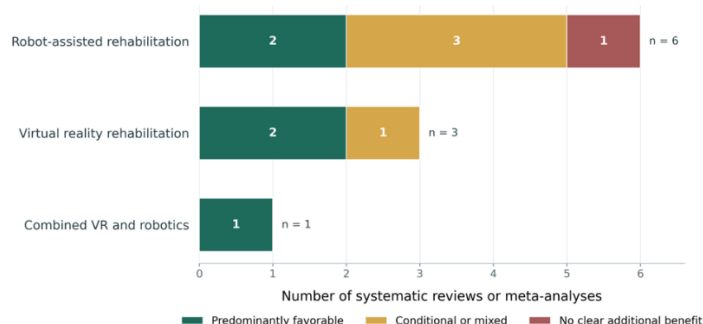
Figure 5.*Direction of findings reported in the systematic reviews and meta-analyses*

Figure 5 summarizes the predominant direction of findings in the 10 systematic reviews and meta-analyses included in the study. The evidence was separated into robot-assisted rehabilitation, virtual reality rehabilitation, and interventions combining virtual reality with robotics.

Each review was classified according to its principal conclusion and the consistency of its reported outcomes:

- * Predominantly favorable: The principal conclusion reported a statistically significant benefit in the main outcome or evidence of positive neuroplastic changes.
- * Conditional or mixed: Benefits were limited to selected outcomes, treatment conditions, time points, patient groups, or intervention parameters. This category also included results indicating equivalence with conventional rehabilitation.
- * No clear additional benefit: The intervention did not demonstrate a statistically significant advantage over the comparison treatment after heterogeneity and uncertainty were considered.

This classification is a descriptive synthesis developed for the present review. It is not a new meta-analysis, and it does not combine effect sizes from outcomes measured with different instruments.

Robot-Assisted Rehabilitation

Six systematic reviews or meta-analyses evaluated robot-assisted rehabilitation. Two—33.3%—were classified as predominantly favorable, three—50%—as conditional or mixed, and one—16.7%—as showing no clear additional benefit.

Bertani et al. (2017) were classified as predominantly favorable because their systematic review concluded that robotic devices positively affected upper-limb recovery after stroke. Their results supported improvements in arm function, although the included studies differed in device type, intervention characteristics, and stroke stage (Bertani et al., 2017).

Tseng et al. (2024) were also placed in the predominantly favorable category because the meta-analysis reported a significant effect of portable robots on upper-limb function measured with the Fugl-Meyer Assessment. The reported standardized mean difference was 0.696, with a confidence interval from 0.099 to 1.293 and a value of p below 0.05. The review included nine studies and 295 participants, with eight studies incorporated into the quantitative analysis (Tseng et al., 2024).

The finding from Tseng et al. was favorable for the principal motor outcome, but the authors also described robotic and conventional rehabilitation as generally comparable. Therefore, its classification reflects the statistically favorable primary quantitative result and does not imply superiority across every clinical domain.

Three robotic reviews were classified as conditional or mixed. Chien et al. (2020) included 11 randomized controlled trials and 493 participants in the subacute stage of stroke. The review reported that robot-assisted therapy produced outcomes comparable with usual care for several measures, while selected improvements were identified in particular functional outcomes. The quality of the evidence was considered low to moderate (Chien et al., 2020).

Veerbeek et al. (2017) were classified as mixed because their meta-analysis reported small but statistically significant improvements in motor control and muscle strength, including an approximate two-point improvement in the upper-extremity Fugl-Meyer score. However, these improvements were not accompanied by significant effects on upper-limb capacity or basic activities of daily living. The direction of the findings therefore differed according to the outcome domain (Veerbeek et al., 2017).

Zhang et al. (2022) also demonstrated a time-dependent pattern. Robot-assisted therapy produced immediate benefits for upper-limb motor control and activity function compared with control interventions. Nevertheless, the authors found insufficient evidence of an additional long-term benefit. The findings were consequently classified as conditional because the positive direction was primarily observed immediately after the intervention and was influenced by treatment duration and active patient participation (Zhang et al., 2022).

The review by Mehrholz et al. (2020) was classified as showing no clear additional benefit. It included 55 randomized controlled trials and 2,654 participants, making it the largest robotic synthesis displayed in Figure 4. After considering heterogeneity and prediction intervals, none of the robotic intervention categories produced statistically significant improvements in activities of daily living, hand-arm function, or arm strength compared with the reference intervention (Mehrholz et al., 2020).

This classification does not mean that participants receiving robotic therapy experienced no improvement. It indicates that the review did not demonstrate a clear additional effect attributable to a specific robotic approach when compared with conventional arm training and after accounting for variation among the studies.

Therefore, five of the six robotic reviews reported at least one favorable result. However, only two were classified as predominantly favorable, while three showed benefits limited by outcome domain, follow-up duration, comparison treatment, or methodological quality.

Virtual Reality Rehabilitation

Three systematic reviews evaluated virtual reality. Two—66.7%—were classified as predominantly favorable, while one—33.3%—was classified as conditional or mixed. None was placed in the no-clear-benefit category.

Hao et al. (2022) were classified as predominantly favorable because the systematic review identified virtual reality—associated changes in neural plasticity. The reported findings included changes in cortical activation, neural-network organization, and functional connectivity. Positive relationships were also identified between neural changes and functional recovery (Hao et al., 2022).

The review by Hao et al. differed from conventional clinical-effectiveness reviews because its principal outcome was neural change rather than a single functional scale. Its favorable classification therefore refers specifically to evidence that virtual reality was associated with measurable neuroplastic responses.

Soleimani et al. (2024) were also classified as predominantly favorable. Their systematic review and meta-analysis incorporated 55 studies and 2,142 participants and reported benefits in upper-limb motor function, functional independence, dexterity, spasticity, and quality of life. The results also varied according to immersion level, treatment duration, and time since stroke (Soleimani et al., 2024).

The updated Cochrane review by Laver et al. (2025) was classified as conditional or mixed. The review indicated that virtual reality may produce slight improvements in upper-limb function and activity, particularly when it increases the total amount of rehabilitation. However, effects differed among outcomes, technologies, and comparison conditions, and many of the included primary studies had small samples (Laver et al., 2025).

The conditional classification of Laver et al. reflects the difference between evidence of a possible benefit and evidence of consistent superiority. It also distinguishes virtual reality used as an additional treatment from virtual reality compared with an equivalent dose of conventional therapy.

Accordingly, all three virtual reality reviews reported some favorable findings, but only two had predominantly positive conclusions for their principal research focus. The Cochrane review presented a more cautious pattern in which benefits were small or dependent on treatment conditions.

Combined Virtual Reality and Robotics

One systematic review and network meta-analysis directly compared virtual reality, robot-assisted rehabilitation, combined interventions, and conventional treatment. It represented 100% of the combined category and was classified as predominantly favorable.

Zhang et al. (2023) included 61 randomized controlled trials and 2,328 participants. The combined robot-assisted and virtual reality intervention had the highest probability of being the most effective option for balance, while virtual reality alone showed the most favorable ranking for daily function. Results for gait were less definitive, and the authors indicated that additional studies were necessary (Zhang et al., 2023).

The favorable classification refers to the principal comparative ranking for balance. It does not demonstrate that combined rehabilitation was superior for every outcome. Furthermore, because only one selected evidence synthesis directly evaluated the combined category, its graphical representation is based on a smaller body of evidence than the robotic or virtual reality categories.

Overall Distribution

Across all 10 systematic reviews and meta-analyses:

- * Five reviews—50%—were classified as predominantly favorable.
- * Four reviews—40%—reported conditional or mixed findings.
- * One review—10%—showed no clear additional benefit.

Thus, nine of the 10 evidence syntheses reported at least one favorable clinical or neuroplasticity-related finding. However, in four of these reviews, the favorable effect was restricted by outcome type, follow-up period, stroke stage, comparison treatment, treatment dose, or methodological quality.

The distribution also differed by technology. Robot-assisted rehabilitation had the largest number of reviews but showed the greatest variation in findings. Virtual reality had fewer evidence syntheses, with two predominantly favorable and one conditional result. Combined virtual reality and robotics had one favorable network meta-analysis but lacked replication across several independent reviews.

Figure 6.

Significant clinical and biological outcomes reported in the randomized trial by Huang et al. (2022)

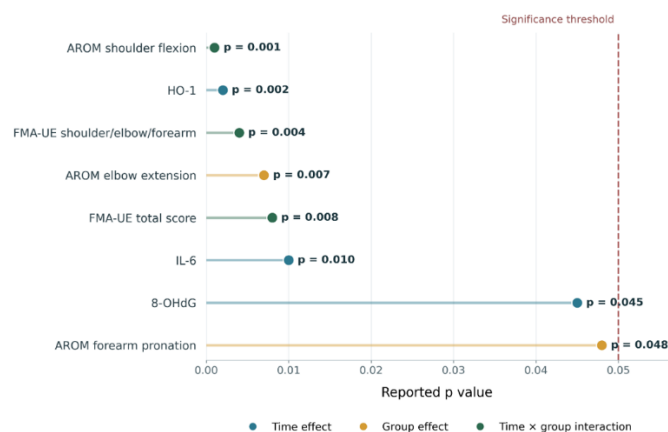


Figure 6 presents the exact statistically significant p values explicitly reported by Huang et al. (2022) in their randomized controlled trial of immersive virtual reality–based motor training in patients with chronic stroke. The study included 30 participants assigned to virtual reality training or conventional occupational therapy.

The investigators assessed upper-limb motor function and serum biomarkers associated with inflammation, oxidative stress, and neuroplasticity. The biological measurements included interleukin 6, heme oxygenase 1, 8-hydroxy-2'-deoxyguanosine, intracellular adhesion molecule 1, and brain-derived neurotrophic factor. Clinical measurements included active range of motion and the upper-extremity Fugl-Meyer Assessment (Huang et al., 2022).

A two-way mixed analysis of variance was used to examine three different statistical components:

- * Time effect: Whether scores changed from before to after treatment when both intervention groups were considered.
- * Group effect: Whether the virtual reality and conventional occupational therapy groups differed when the assessment times were considered together.
- * Time-by-group interaction: Whether the pattern of change over time differed between the two treatment groups.

These three effects address different questions and should not be treated as interchangeable. In particular, a significant time effect does not demonstrate that virtual reality was superior because both groups may have improved. A significant interaction provides more direct statistical evidence that the change followed a different pattern according to the assigned intervention.

Time Effects

Three biomarkers showed significant time effects: heme oxygenase 1, interleukin 6, and 8-hydroxy-2'-deoxyguanosine.

Heme Oxygenase 1

Heme oxygenase 1 demonstrated a significant time effect with $p = 0.002$. This was the lowest p value among the three biomarkers with reported significant changes over time.

Heme oxygenase 1 is an inducible enzyme involved in cellular responses to oxidative stress. The statistical result indicates that its serum level changed significantly across the assessment period when the two treatment groups were

considered together. However, because this was a time effect rather than a time-by-group interaction, the result does not establish that immersive virtual reality produced a greater change than conventional occupational therapy.

Interleukin 6

Interleukin 6 showed a significant time effect with $p = 0.010$. IL-6 is an inflammatory cytokine whose concentration may change in response to neurological injury, systemic inflammation, physical activity, and rehabilitation.

The result indicates a statistically detectable change over time in the overall study sample. The graph does not represent the direction of the change, its magnitude, or its clinical relevance. These aspects require the group means, dispersion measures, and confidence intervals reported in the original trial.

8-Hydroxy-2'-Deoxyguanosine

The oxidative stress marker 8-OHdG demonstrated a significant time effect with $p = 0.045$. This value was below the predefined threshold of 0.05 but closer to that limit than the findings for HO-1 and IL-6.

As with the other biomarkers, the significant time effect indicates that the measurement changed during the intervention period across the groups. It does not demonstrate a specific effect attributable exclusively to virtual reality.

The three significant biomarker results therefore document biological changes during the rehabilitation period. However, none of the values displayed in the time-effect category independently establishes a between-group difference.

Group Effects

Two active-range-of-motion measurements demonstrated significant group effects: elbow extension and forearm pronation.

Active Elbow Extension

Active range of motion in elbow extension showed a significant group effect with $p = 0.007$. This indicates a difference between the virtual reality and conventional occupational therapy groups when the measurement times were considered within the statistical model.

The finding was more statistically distinct from the 0.05 threshold than the group effect observed for forearm pronation. Nevertheless, it does not provide the number of degrees gained, the size of the between-group difference, or whether that difference exceeded a clinically meaningful threshold.

Active Forearm Pronation

Active forearm pronation demonstrated a group effect with $p = 0.048$. This was the value closest to the 0.05 threshold among the eight findings displayed in the figure.

The result met the conventional criterion for statistical significance used in the study. However, its proximity to the threshold and the relatively small sample require cautious descriptive reporting. The p value alone does not provide information about precision or effect size.

Neither group effect should be interpreted as proof that all upper-limb movements responded differently to virtual reality. The reported differences were specific to elbow extension and forearm pronation.

Time-by-Group Interactions

Three clinical outcomes demonstrated significant time-by-group interactions: active shoulder flexion, the shoulder/elbow/forearm section of the Fugl-Meyer Assessment, and the total Fugl-Meyer upper-extremity score.

Active Shoulder Flexion

Active shoulder flexion showed the smallest reported p value in the figure, with $p = 0.001$. The significant interaction indicates that the pattern of change in shoulder flexion differed between the virtual reality and conventional occupational therapy groups.

Because this was an interaction rather than only a time or group effect, it provides the most direct statistical evidence in the study that the intervention groups followed different recovery trajectories for this specific movement.

Fugl-Meyer Shoulder, Elbow, and Forearm Subscale

The shoulder/elbow/forearm component of the upper-extremity Fugl-Meyer Assessment demonstrated a significant interaction with $p = 0.004$. This subscale evaluates coordinated motor performance in proximal segments of the affected upper limb.

The interaction indicates that changes in this motor domain differed according to treatment group. This result is consistent with the significant interaction reported for active shoulder flexion, since both measurements include proximal upper-limb performance.

Total Fugl-Meyer Upper-Extremity Score

The total Fugl-Meyer upper-extremity score showed a significant interaction with $p = 0.008$. This finding indicates that the overall motor-impairment trajectory differed between the two groups over time.

The total score integrates multiple upper-limb motor components and therefore provides a broader assessment than an isolated joint movement. However, the p value does not indicate the number of Fugl-Meyer points gained or whether the between-group difference reached the minimal clinically important difference.

All three significant interactions corresponded to clinical motor or movement outcomes. In contrast, the explicitly reported significant biomarker findings were time effects rather than time-by-group interactions.

Outcomes Not Represented in the Figure

The study assessed additional variables that are not displayed because the graph was restricted to exact statistically significant p values reported in the abstract. The absence of a variable from the figure does not mean that it was not measured.

Brain-derived neurotrophic factor was evaluated as a potential indicator of neuroplasticity, but no significant group-specific result was reported among the principal abstract findings. Similarly, the Fugl-Meyer coordination and speed component did not reach the conventional threshold for a time effect, with $p = 0.055$.

Therefore, the study demonstrated significant clinical interactions but did not provide equivalent evidence of a differential BDNF response attributable to virtual reality. The biological findings primarily reflected changes over time across both rehabilitation groups.

Overall Statistical Pattern

Of the eight significant findings displayed:

- * Three—37.5%—were time effects.
- * Two—25%—were group effects.
- * Three—37.5%—were time-by-group interactions.

The three time-by-group interactions involved clinical motor measurements. The three time effects involved serum biomarkers. The two group effects involved active range of motion.

This distribution separates the evidence into two patterns. First, biological changes occurred during the rehabilitation period but were not reported as specifically greater in the virtual reality group. Second, selected proximal upper-limb and total motor-function measurements followed different trajectories according to treatment assignment.

The figure intentionally displays p values rather than effect sizes because the purpose is to reproduce the statistical findings reported in the trial. A lower p value should not be interpreted as a larger therapeutic benefit. Clinical magnitude requires mean differences, standardized effects, confidence intervals, and minimal clinically important differences.

Furthermore, the study evaluated numerous biomarkers and clinical outcomes. Figure 6 does not apply an additional correction for multiple comparisons beyond the analyses reported by the original investigators. The findings should therefore be presented as results from a small randomized exploratory study rather than definitive estimates for the complete post-stroke population.

Figure 7.

Frequency of outcome domains evaluated across the systematic reviews and meta-analyses

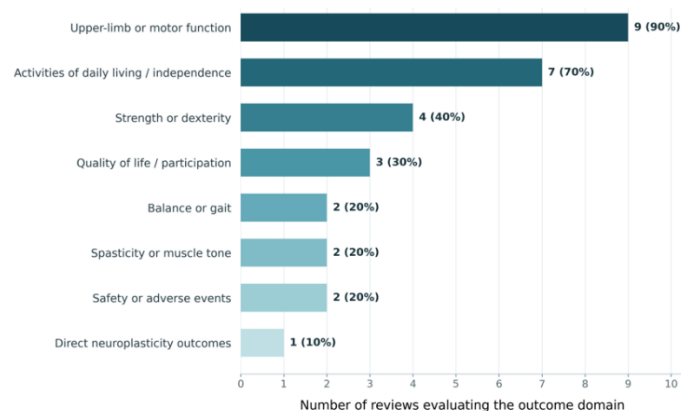


Figure 7 presents the frequency with which eight outcome domains were evaluated across the 10 systematic reviews and meta-analyses included in the study. Unlike the preceding figures, the categories are not mutually exclusive. A single review could be counted in several domains if it explicitly evaluated more than one type of outcome.

For example, a publication assessing upper-limb motor function, activities of daily living, muscle strength, and safety was counted once in each of those four categories. Consequently, the frequencies should not be added together to calculate the number of publications.

The figure measures the representation of each outcome within the selected evidence syntheses. It does not indicate whether the result was statistically significant or favorable.

Upper-Limb or Motor Function

Upper-limb or general motor function was the most frequently evaluated domain. It appeared in nine of the 10 systematic reviews and meta-analyses, corresponding to 90%.

This category included outcomes measured with instruments such as:

- * Fugl-Meyer Assessment for the upper extremity.
- * Wolf Motor Function Test.
- * Action Research Arm Test.
- * Box and Block Test.
- * Upper-limb range of motion.
- * Motor-control and arm-function scales.
- * Device-specific movement measurements.

Motor outcomes were evaluated in the robotic syntheses by Bertani et al. (2017), Chien et al. (2020), Mehrholz et al. (2020), Tseng et al. (2024), Veerbeek et al. (2017), and Zhang et al. (2022). They were also included in the virtual reality reviews by Hao et al. (2022), Laver et al. (2025), and Soleimani et al. (2024).

The high frequency reflects the predominant clinical focus of digital stroke rehabilitation on restoring movement of the affected upper limb. Robotic systems are commonly designed to assist reaching, shoulder and elbow movement,

wrist control, grasping, or hand opening. Virtual reality systems similarly use reaching, object manipulation, coordination, and task-completion exercises.

However, the presence of motor function as an outcome does not mean that all nine reviews reported equivalent benefits. Mehrholz et al. did not find a statistically significant advantage for hand-arm function after heterogeneity was considered. Veerbeek et al. found small improvements in motor control but no corresponding improvement in upper-limb capacity. Soleimani et al. reported broader favorable effects across several upper-limb domains (Mehrholz et al., 2020; Veerbeek et al., 2017; Soleimani et al., 2024).

Activities of Daily Living and Functional Independence

Activities of daily living or functional independence were evaluated in seven reviews, equivalent to 70%. This was the second most frequently represented outcome domain.

The category included measurements related to:

- * Feeding.
- * Dressing.
- * Grooming.
- * Personal hygiene.
- * Transfers.
- * Mobility.
- * Basic self-care.
- * Barthel Index.
- * Functional Independence Measure.
- * Stroke Impact Scale.
- * Other standardized activity measures.

This domain was reported in the reviews by Chien et al. (2020), Laver et al. (2025), Mehrholz et al. (2020), Soleimani et al. (2024), Veerbeek et al. (2017), Zhang et al. (2022), and Zhang et al. (2023).

The distinction between motor impairment and activities of daily living is important for describing the results. A patient may improve movement quality or strength without achieving a corresponding increase in independent daily activity. This pattern was observed in Veerbeek et al. (2017), who reported small improvements in motor control and strength but no significant effects on basic activities of daily living.

Zhang et al. (2022) found immediate benefits of robot-assisted therapy for motor control and activity function but insufficient evidence of an additional long-term benefit. Zhang et al. (2023) reported that virtual reality had the most favorable ranking for daily function within their network comparison (Zhang et al., 2022; Zhang et al., 2023).

Thus, although activities of daily living were assessed in most reviews, they were evaluated less frequently than impairment-based motor outcomes.

Strength or Dexterity

Muscle strength or manual dexterity was explicitly evaluated in four reviews, corresponding to 40%. This category included grip strength, paretic-arm strength, hand control, fine motor performance, and manipulation tests.

The domain was represented by Laver et al. (2025), Mehrholz et al. (2020), Soleimani et al. (2024), and Veerbeek et al. (2017).

Mehrholz et al. included arm strength as a secondary endpoint but did not identify a statistically significant advantage after accounting for heterogeneity. Veerbeek et al. reported a small significant improvement in muscle strength. Soleimani et al. reported favorable results for dexterity, with differences depending on the level of virtual reality immersion (Mehrholz et al., 2020; Soleimani et al., 2024).

Strength and dexterity were grouped in the figure because both relate to upper-limb performance, although they represent different constructs. Strength measures force production, whereas dexterity reflects speed, precision, coordination, and object manipulation.

Quality of Life or Participation

Quality of life, health status, or social participation was evaluated in three reviews, equivalent to 30%. These outcomes examine the effect of rehabilitation beyond motor impairment and basic independence.

The category included measures of:

- * Perceived physical function.
- * Emotional well-being.
- * Social participation.
- * Stroke-related quality of life.
- * Health-related quality of life.
- * Community reintegration.

The three reviews contributing to this domain were those by Chien et al. (2020), Laver et al. (2025), and Soleimani et al. (2024). Soleimani et al. reported favorable virtual reality results for quality of life, while the broader evidence reviewed by Laver et al. was more limited and heterogeneous.

Only three of the 10 evidence syntheses included this outcome domain, despite its relevance to long-term stroke recovery. The figure records its lower representation without determining the reason for its less frequent use.

Balance or Gait

Balance or gait outcomes appeared in two reviews, corresponding to 20%. These outcomes included postural stability, functional balance, walking capacity, and gait-related measures.

The domain was evaluated in the broad virtual reality review by Laver et al. (2025) and the network meta-analysis by Zhang et al. (2023). Zhang et al. specifically compared the effects of robotics, virtual reality, combined therapy, and conventional treatment on balance, gait, and daily function.

The combined robot-assisted and virtual reality intervention achieved the most favorable ranking for balance in Zhang et al. However, the evidence for gait was less definitive, and the authors identified a need for additional studies (Zhang et al., 2023).

The low frequency of balance and gait outcomes is partly related to the thematic composition of the selected evidence: most robotic publications focused on the upper limb rather than lower-limb or gait-training systems.

Spasticity or Muscle Tone

Spasticity or muscle tone was evaluated in two reviews, equivalent to 20%. Soleimani et al. (2024) assessed spasticity among the outcomes of virtual reality-based upper-limb rehabilitation, while Veerbeek et al. (2017) evaluated muscle tone within robot-assisted therapy.

Veerbeek et al. reported a negative effect on muscle tone despite small favorable effects on motor control and strength. This difference demonstrates that treatment effects were not uniformly favorable across all impairment domains. Soleimani et al. reported favorable results for spasticity within their broader meta-analysis of virtual reality outcomes (Veerbeek et al., 2017; Soleimani et al., 2024).

Spasticity was considered separately from motor function because a reduction in muscle tone does not necessarily produce an equivalent improvement in voluntary movement or daily activity.

Safety or Adverse Events

Safety or adverse events were explicitly evaluated in two reviews, corresponding to 20%. This category included pain, dizziness, headache, feeling faint, falls, treatment-related discomfort, serious adverse events, and discontinuation associated with the intervention.

Mehrholz et al. (2020) included safety as a secondary endpoint in robotic rehabilitation. Laver et al. (2025) evaluated adverse events associated with virtual reality. The Cochrane review reported a small number of events such as pain, headache, dizziness, or feeling faint, with no serious unwanted effects identified in the summarized evidence (Laver et al., 2025).

The figure counts only reviews that explicitly incorporated safety or adverse-event assessment. A review not counted in this category should not automatically be interpreted as having found the intervention safe; it may not have systematically evaluated or reported adverse outcomes.

Direct Neuroplasticity Outcomes

Direct neuroplasticity outcomes were evaluated in one systematic review, representing 10%. This category was restricted to measurements of neural changes rather than clinical outcomes theoretically associated with plasticity.

Hao et al. (2022) examined:

* Cortical activation.

- * Functional connectivity.
- * Changes in brain-network organization.
- * Cortical reorganization.
- * Neurophysiological responses.
- * Relationships between neural changes and functional recovery.

The review found virtual reality–associated neural changes and positive relationships between several neuroplasticity measurements and functional improvement (Hao et al., 2022).

Although neuroplasticity is central to the theoretical rationale for digital rehabilitation, it was directly evaluated in only one of the 10 evidence syntheses. The remaining reviews primarily inferred neuroplastic potential from improvements in motor or functional performance rather than measuring neural adaptation directly.

Overall Distribution

The figure demonstrates a descending pattern from impairment-based outcomes toward broader or mechanistic outcomes:

- * Motor function: 90%.
- * Activities and independence: 70%.
- * Strength or dexterity: 40%.
- * Quality of life or participation: 30%.
- * Balance or gait: 20%.
- * Spasticity or tone: 20%.
- * Safety: 20%.
- * Direct neuroplasticity: 10%.

The findings synthesized in this review reinforce the growing recognition of clonal hematopoiesis as a central biological process linking aging, cardiovascular disease, and hematologic malignancies. Rather than representing an incidental molecular finding, clonal hematopoiesis has emerged as an important determinant of systemic health, providing a mechanistic explanation for the increased burden of inflammatory and neoplastic diseases observed during aging. The progressive increase in prevalence across older age groups identified in the reviewed evidence is consistent with the cumulative acquisition of somatic mutations in hematopoietic stem cells and confirms that aging constitutes the principal biological driver of clonal expansion (Jaiswal et al., 2014; Genovese et al., 2014).

One of the most relevant observations of this review is the predominance of **DNMT3A**, **TET2**, and **ASXL1** mutations among individuals with clonal hematopoiesis. These genes participate in epigenetic regulation, highlighting that alterations in chromatin remodeling and DNA methylation are fundamental mechanisms underlying age-associated clonal selection. This observation agrees with previous genomic studies demonstrating that disruption of epigenetic homeostasis precedes the development of many hematologic disorders and may also contribute to chronic inflammatory activation before overt malignant transformation becomes clinically evident (Buscarlet et al., 2017; Steensma et al., 2015).

The reviewed evidence also demonstrates that the clinical consequences of clonal hematopoiesis extend far beyond hematologic oncology. Historically, somatic mutations detected in blood cells were primarily interpreted as indicators of leukemia risk. However, current evidence indicates that cardiovascular complications occur more frequently than progression to hematologic malignancy among individuals with CHIP. This shift has transformed the clinical significance of clonal hematopoiesis, positioning it as a relevant cardiovascular risk modifier that complements conventional factors such as hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking (Jaiswal et al., 2017).

The biological mechanisms supporting this association are increasingly well established. Experimental studies consistently demonstrate that mutant hematopoietic clones alter innate immune responses through excessive production of inflammatory cytokines, activation of the NLRP3 inflammasome, endothelial dysfunction, and accelerated atherosclerotic plaque formation. These mechanisms provide a convincing explanation for the higher frequencies of coronary artery disease, myocardial infarction, ischemic stroke, heart failure, and cardiovascular mortality observed among CHIP carriers in multiple international cohorts. The convergence of molecular, experimental, and epidemiological evidence substantially strengthens the hypothesis that clonal hematopoiesis actively contributes to cardiovascular disease rather than serving solely as a marker of biological aging (Fuster et al., 2017; Libby & Jaiswal, 2019).

Another important finding concerns the heterogeneous biological behavior of individual mutations. The reviewed literature indicates that not all driver mutations confer identical clinical risks. **TET2** and **DNMT3A** mutations appear to exert their principal effects through inflammatory pathways, whereas **JAK2** mutations show a stronger association with thrombotic complications due to activation of the JAK–STAT pathway, platelet activation, and neutrophil extracellular trap formation. In contrast, mutations involving **TP53** and **PPM1D** are more closely associated with therapy-related clonal expansion and progression toward myeloid malignancies. These observations emphasize that mutation-specific biology should be considered when estimating prognosis and designing future individualized management strategies (Tall & Fuster, 2022; Coombs et al., 2017).

The analysis also highlights the importance of **clone size**, represented by variant allele frequency, as an additional determinant of clinical outcomes. Larger mutant clones generally exhibit greater inflammatory activity and are more frequently associated with adverse cardiovascular events and hematologic progression. This finding suggests that quantitative molecular parameters may eventually complement traditional clinical evaluation, allowing more refined risk stratification based on both genetic composition and clonal burden (Bick et al., 2020).

Despite these advances, several limitations remain evident in the current body of evidence. Most available studies originate from North American and European populations, while data from Latin America, Africa, and other underrepresented regions remain comparatively limited. Differences in genetic ancestry, environmental exposures, healthcare access, and socioeconomic conditions may influence both mutation prevalence and disease expression. Consequently, greater participation of Latin American research groups will be essential to determine whether currently available risk estimates can be generalized across diverse populations and healthcare systems.

Another important limitation involves the absence of universally accepted clinical management guidelines. Although next-generation sequencing has greatly improved the detection of CHIP-associated mutations, uncertainty persists regarding the appropriate timing of molecular testing, optimal surveillance intervals, interpretation of low variant allele frequencies, and indications for preventive therapeutic interventions. Similarly, routine population-wide screening cannot currently be recommended because evidence demonstrating clinical benefit remains insufficient. Future prospective clinical trials will be required to establish standardized management algorithms based on mutation profile, clone size, and overall cardiovascular and hematologic risk.

The emerging role of precision medicine represents one of the most promising future directions identified during this review. Integration of genomic information with inflammatory biomarkers, imaging studies, cardiovascular risk scores, and artificial intelligence-based predictive models may facilitate earlier identification of individuals at greatest risk of adverse outcomes. Such multidisciplinary approaches have the potential to improve personalized prevention, optimize long-term surveillance, and support the development of targeted anti-inflammatory or mutation-specific therapeutic strategies.

Figure 8.

Relationship between the number of included studies and participants in selected evidence syntheses

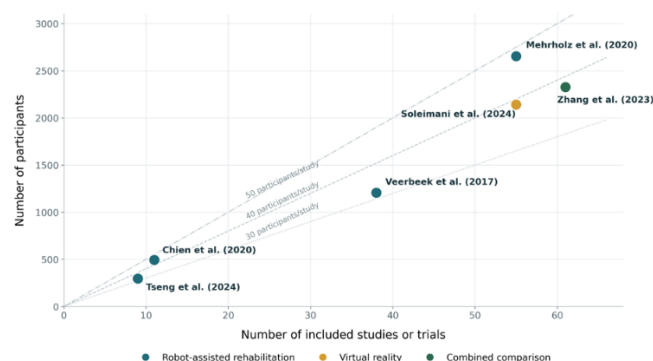


Figure 8 presents the relationship between the number of primary studies and the total number of participants reported in six systematic reviews and meta-analyses. The horizontal axis represents the number of included studies or randomized trials, while the vertical axis represents the corresponding participant sample.

The diagonal reference lines indicate approximate ratios of 30, 40, and 50 participants per included study. These lines are descriptive references rather than statistical regression models or methodological quality thresholds. They make it possible to compare the approximate average size of the primary studies incorporated into each evidence synthesis.

Mehrholtz et al. (2020) reported the largest participant sample, with 2,654 individuals distributed across 55 randomized controlled trials. This corresponds to approximately 48.3 participants per trial, placing the publication close to the reference line of 50 participants per study.

The network meta-analysis evaluated different forms of electromechanical and robot-assisted arm training. Despite having the largest participant sample in the figure, the authors did not find statistically significant advantages for the robotic intervention categories in activities of daily living, hand-arm function, or arm strength after heterogeneity was considered. Its position in the graph therefore represents the volume of evidence analyzed and not the effectiveness of the intervention (Mehrholtz et al., 2020).

Zhang et al. (2023) included the largest number of randomized controlled trials, with 61 studies and 2,328 participants. The approximate ratio was 38.2 participants per trial. Although this review included six more trials than Mehrholtz et al. (2020), its total sample was 326 participants smaller, indicating that the primary studies were smaller on average.

This network meta-analysis compared robot-assisted rehabilitation, virtual reality, combined technological interventions, and conventional therapy. The combined intervention obtained the most favorable ranking for balance, whereas virtual reality showed a favorable ranking for daily function. Findings for gait were less definitive (Zhang et al., 2023).

Soleimani et al. (2024) analyzed 55 studies involving 2,142 participants, corresponding to approximately 38.9 participants per study. The publication therefore appears close to the reference line of 40 participants per study.

Although Soleimani et al. (2024) and Mehrholtz et al. (2020) included the same number of studies, the former analyzed 512 fewer participants. The difference reflects variation in the size of the primary studies and in the characteristics of the eligible populations.

Soleimani et al. (2024) focused on virtual reality for upper-limb rehabilitation and reported favorable results in motor function, dexterity, functional independence, spasticity, and quality of life. Differences were also observed according to immersion level, intervention duration, and time since stroke.

Veerbeek et al. (2017) included 38 trials and 1,206 participants, corresponding to approximately 31.7 participants per trial. The publication is therefore located slightly above the reference line of 30 participants per study.

The review reported small statistically significant improvements in upper-limb motor control and muscle strength. However, these improvements were not accompanied by significant effects on upper-limb capacity or basic activities of daily living. Its intermediate position reflects a smaller evidence base than the three preceding syntheses, while still incorporating more than 1,000 participants (Veerbeek et al., 2017).

Chien et al. (2020) analyzed 11 randomized controlled trials involving 493 participants. This represents approximately 44.8 participants per trial, placing the publication between the reference lines of 40 and 50 participants per study.

Although the pooled sample was smaller than those of Mehrholz et al. (2020), Zhang et al. (2023), Soleimani et al. (2024), and Veerbeek et al. (2017), its average number of participants per trial was comparatively high. The smaller number of trials partly reflects its specific focus on patients in the subacute stage of stroke.

The review classified the available evidence as low to moderate in quality. Robot-assisted therapy produced results generally comparable with usual care, although selected functional benefits were reported (Chien et al., 2020).

Tseng et al. (2024) presented the smallest evidence synthesis in the figure, with nine studies and 295 participants. The approximate ratio was 32.8 participants per study, placing the publication slightly above the reference line of 30 participants per study.

The smaller evidence base is consistent with the review's specific focus on portable upper-limb robots rather than all robotic rehabilitation systems. Eight of the nine identified studies were incorporated into the quantitative analysis.

The authors reported a statistically significant standardized effect for upper-limb function measured with the Fugl-Meyer Assessment. Nevertheless, portable robotic rehabilitation and conventional therapy were described as generally comparable, with favorable results observed in selected studies (Tseng et al., 2024).

Overall, the graph shows a positive descriptive relationship between the number of included studies and the number of participants. Reviews containing more primary studies generally incorporated larger pooled samples. However, the relationship was not proportional because the average size of the primary trials differed among publications.

Mehrholz et al. (2020) had the highest approximate participant-per-trial ratio, with 48.3, followed by Chien et al. (2020), with 44.8. Soleimani et al. (2024) and Zhang et al. (2023) reported approximately 38.9 and 38.2 participants per study, respectively. Tseng et al. (2024) included approximately 32.8 participants per study, while Veerbeek et al. (2017) had the lowest ratio, with approximately 31.7 participants per trial.

The ratios ranged from approximately 31.7 to 48.3 participants per primary study. None of the six evidence syntheses reached an average above 50 participants per included study.

These results indicate that the large pooled samples were constructed from numerous primary studies that were generally small. However, the participant-per-study ratio is only a crude average and does not describe the actual distribution of sample sizes. A systematic review may combine several very small studies with a limited number of larger trials.

The figure also demonstrates that evidence volume and result direction are not equivalent. Mehrholz et al. (2020) analyzed the largest participant sample but did not demonstrate a clear additional benefit from a specific robotic approach. Conversely, Tseng et al. (2024) included the smallest sample but reported a statistically significant effect for their principal motor outcome.

Differences in conclusions cannot therefore be explained solely by the number of trials or participants. Other relevant factors include the type of technology, treatment dose, stage of stroke, baseline severity, degree of active participation, comparator intervention, outcome instrument, follow-up duration, statistical heterogeneity, and methodological quality.

DISCUSIÓN

The findings of this integrative review indicate that virtual reality and robot-assisted rehabilitation can contribute to post-stroke motor and functional recovery. However, their effects are heterogeneous and are influenced by treatment intensity, technological characteristics, stroke stage, patient selection, comparison therapy, and the outcome evaluated.

Of the 10 systematic reviews and meta-analyses examined, five presented predominantly favorable conclusions, four reported conditional or mixed results, and one found no clear additional benefit. Therefore, the evidence supports the use of digital technologies as complementary rehabilitation tools, but it does not demonstrate their universal superiority over conventional therapy.

Digital Rehabilitation and Neuroplasticity

The biological rationale for digital neurorehabilitation is consistent with the established principles of experience-dependent neuroplasticity. Recovery after stroke involves changes in cortical excitability, synaptic strength, functional connectivity, interhemispheric interactions, and recruitment of surviving neural networks. These processes can be influenced by intensive, repetitive, task-specific, progressively challenging, and meaningful practice (Dimyan & Cohen, 2011; Di Pino et al., 2014).

Virtual reality and robotics can operationalize these principles by increasing movement repetitions, controlling task difficulty, providing immediate feedback, and quantifying performance. However, the presence of technology does not automatically produce adaptive neuroplasticity. The therapeutic activity must require voluntary effort, error correction, attention, motivation, and progressive adaptation.

A repetitive movement performed passively or without functional meaning may produce less motor learning than an actively executed task connected to an achievable and clinically relevant goal. Digital technologies should therefore be considered instruments for delivering rehabilitation principles rather than independent therapeutic mechanisms (Krakauer et al., 2012; Mang et al., 2013).

Hao et al. (2022) identified changes in cortical activation, functional connectivity, and brain-network organization following virtual reality interventions. Positive relationships were also reported between neural changes and functional recovery. These findings support the neuroplastic potential of virtual rehabilitation.

Nevertheless, differences in neuroimaging techniques, intervention protocols, treatment doses, and stroke stages limit direct comparisons among studies. Increased activation in a brain region does not always represent functional restitution. It may also indicate compensation or inefficient recruitment of secondary networks.

Neuroplastic changes should therefore be interpreted together with movement quality, functional independence, activities of daily living, and real-world use of the affected limb. Cerebral activation alone cannot establish clinically meaningful recovery.

Effectiveness of Virtual Reality

The evidence concerning virtual reality was generally favorable but not uniform. Soleimani et al. (2024) reported benefits in upper-limb motor function, functional independence, dexterity, spasticity, and quality of life across 55 studies involving 2,142 participants.

The authors also found that immersion level, intervention duration, and time since stroke influenced the outcomes. Fully immersive systems appeared particularly useful for gross motor function, whereas non-immersive systems showed benefits in fine dexterity (Soleimani et al., 2024).

These findings demonstrate that virtual reality should not be considered a single homogeneous intervention. Non-immersive games, camera-based movement systems, projection environments, and head-mounted displays deliver different levels of sensory stimulation, presence, movement freedom, and task complexity.

Combining all virtual reality systems into one analytical category may conceal clinically relevant differences. Effectiveness may depend more on the therapeutic content, treatment dose, active participation, and feedback than on the technological level of immersion alone.

The updated Cochrane review presented a more cautious conclusion. Laver et al. (2025) found that virtual reality may produce slight improvements in upper-limb function and activity, particularly when it increases the total amount of rehabilitation. However, the results varied among outcomes, technologies, and comparison conditions, and many primary studies had small samples.

The differences between the conclusions of Soleimani et al. (2024) and Laver et al. (2025) may be explained by variations in eligibility criteria, outcome selection, statistical models, and intervention classification. A review focused specifically on upper-limb virtual reality may identify favorable effects that become less consistent when virtual reality is evaluated across a wider range of functions and technological systems.

The distinction between adjunctive and substitutive use is particularly important. When virtual reality is added to usual care, patients receive more rehabilitation time than the control group. Under these conditions, additional improvement may result partly from increased practice rather than a specific virtual reality effect.

Dose-matched studies provide a more rigorous assessment of whether virtual reality produces greater benefits than an equivalent amount of conventional treatment. The available evidence suggests that virtual reality is particularly useful for expanding practice, engagement, motivation, and feedback. Its ability to replace therapist-directed rehabilitation or consistently outperform equally intensive conventional therapy remains uncertain.

Effectiveness of Robot-Assisted Rehabilitation

Robot-assisted rehabilitation showed greater variability in its results. Bertani et al. (2017) concluded that robotic devices could positively influence upper-limb recovery. Tseng et al. (2024) reported a significant standardized effect of portable robots on upper-limb motor function measured with the Fugl-Meyer Assessment.

These findings support the capacity of robotic systems to deliver intensive, repetitive, measurable, and standardized movement training. However, not all evidence syntheses reached the same conclusion.

Mehrholz et al. (2020) analyzed 55 randomized controlled trials involving 2,654 participants and found no statistically significant advantage for the robotic intervention categories after heterogeneity was considered. This was the largest robotic participant sample analyzed in the results, showing that a broader evidence base does not necessarily produce a more favorable conclusion.

Veerbeek et al. (2017) identified small improvements in motor control and muscle strength but no significant effect on upper-limb capacity or basic activities of daily living. This discrepancy illustrates the difference between changes at the impairment level and functional transfer.

A patient may improve strength, range of motion, or movement control during a structured assessment without using the affected limb more effectively in daily activities. Therefore, improvement on a motor scale should not automatically be interpreted as greater independence.

Zhang et al. (2022) similarly reported immediate benefits in motor control and activity function but found insufficient evidence of additional long-term effects. These results suggest that robotic improvements may diminish after supervised treatment ends unless the acquired movements are incorporated into meaningful daily activities.

One possible explanation is that robotic devices frequently emphasize highly controlled and predictable movement trajectories. This may improve the specific movement practiced with the device while providing fewer opportunities for variable, context-dependent motor problem-solving.

Functional transfer may require combining robotic repetitions with object manipulation, self-care activities, environmental variability, bilateral tasks, and spontaneous use of the affected extremity.

The degree of robotic assistance is also relevant. Excessive assistance may reduce voluntary effort, attention, sensory prediction, and error processing. An assist-as-needed approach is more consistent with motor-learning principles because it provides sufficient support to complete the movement while preserving active participation.

Robotic assistance should be progressively reduced as the patient improves. Robots may be most useful when their physical support is combined with functional goals and therapist-directed activities.

Combined Virtual Reality and Robotics

The integration of virtual reality and robotics may combine the physical capabilities of robotic devices with the motivational and sensory characteristics of virtual environments. Robotics can provide physical assistance, resistance, movement guidance, and haptic feedback, while virtual reality can create meaningful goals and immediate visual or auditory responses.

Zhang et al. (2023) found that combined robot-assisted and virtual reality training had the highest probability of being the most effective intervention for balance. Virtual reality alone showed the most favorable ranking for daily function. Nevertheless, the evidence for gait was less definitive.

The favorable result should be interpreted as promising rather than conclusive. The combined category was represented by only one selected evidence synthesis. Furthermore, network meta-analysis incorporates direct and indirect comparisons, meaning that not every intervention pair was necessarily evaluated within the same randomized controlled trial.

Additional direct comparisons are required to establish whether the combination provides benefits beyond either technology used independently.

The combined approach may be especially useful when robotic movement directly controls a meaningful virtual task. For example, reaching with robotic assistance to manipulate a virtual object may be more functionally relevant than repeatedly following a predetermined trajectory without an external goal.

Clinical Versus Statistical Significance

A central finding of the review is that statistically significant outcomes do not necessarily indicate clinically meaningful recovery. Veerbeek et al. (2017) reported an approximate two-point improvement in the upper-extremity Fugl-Meyer Assessment. However, the functional relevance of such a small difference is uncertain.

The significant findings reported by Huang et al. (2022) should also be interpreted beyond their p values. Their trial demonstrated significant time-by-group interactions for active shoulder flexion, the proximal Fugl-Meyer subscale, and the total Fugl-Meyer upper-extremity score.

However, a smaller p value does not indicate a larger therapeutic benefit. Clinical interpretation requires mean differences, effect sizes, confidence intervals, and minimal clinically important differences.

This distinction is especially relevant in small studies. A statistically significant result may be unstable or imprecise, whereas a clinically relevant difference may fail to reach statistical significance when the sample is insufficient.

Future studies should report statistical and clinical indicators simultaneously. Long-term follow-up should also be included to determine whether observed improvements remain after the intervention concludes.

Biomarkers and Neural Mechanisms

Huang et al. (2022) identified significant time effects for heme oxygenase 1, interleukin 6, and 8-hydroxy-2'-deoxyguanosine. These findings indicate biological changes during the rehabilitation period.

However, the findings represented time effects across both treatment groups rather than time-by-group interactions demonstrating a specific virtual reality effect. Therefore, these biological changes cannot be attributed exclusively to immersive virtual reality.

Brain-derived neurotrophic factor was measured as a potential marker of neuroplasticity but did not show a significant intervention-specific result among the principal findings. The trial consequently provided stronger evidence of differential clinical motor changes than of a unique biomarker response caused by virtual reality.

Biomarkers such as BDNF, inflammatory cytokines, and oxidative stress markers can be influenced by age, medications, metabolic conditions, physical activity, sleep, diet, stress, and stroke characteristics. Future studies should control these variables and combine serum measurements with neuroimaging and neurophysiological evaluations.

Treatment Dose and Timing

The effectiveness of digital rehabilitation appears to depend substantially on treatment dose. Soleimani et al. (2024) reported better outcomes with interventions lasting more than six weeks and when virtual reality began within six months after stroke.

Laver et al. (2025) similarly indicated that virtual reality may be more beneficial when it increases the total number of rehabilitation hours. These results are consistent with the principles of experience-dependent plasticity, which require sufficient repetition and intensity.

Nevertheless, more treatment is not automatically better for every patient. Excessive intensity can cause fatigue, pain, frustration, reduced adherence, or compensatory movement patterns. Dose should be individualized according to medical stability, neurological impairment, exercise tolerance, cognition, and treatment response.

The subacute stage may represent a particularly responsive period because spontaneous biological recovery and neuroplasticity are more active. However, patients may also experience medical instability, severe weakness, fatigue, or reduced attention.

Chien et al. (2020) found that robot-assisted rehabilitation in subacute stroke produced outcomes generally comparable with usual care, with selected benefits and low-to-moderate evidence quality.

Patients with chronic stroke may also improve following virtual or robotic training. However, they may require greater intensity, longer intervention periods, and explicit strategies to transfer improvements into everyday activities.

Patient Selection and Personalization

No single digital rehabilitation system is appropriate for all stroke survivors. Patient selection should consider:

- Baseline motor impairment.
- Stroke severity.
- Lesion location.
- Corticospinal tract integrity.
- Time since stroke.
- Cognitive and communicative abilities.
- Visual or perceptual deficits.
- Unilateral neglect.
- Fatigue.
- Spasticity and pain.
- Digital literacy.
- Motivation and treatment preferences.

- Risk of dizziness or cybersickness.

Patients with severe weakness may benefit from robotic assistance that enables movement practice. Patients with greater voluntary control may obtain more benefit from challenging virtual activities with reduced physical assistance.

Treatment should also be adapted throughout recovery. Assistance, task difficulty, range of motion, feedback frequency, and exercise complexity should change according to patient performance.

Safety and Acceptability

Safety or adverse events were explicitly evaluated in only two of the 10 evidence syntheses. Laver et al. (2025) identified a small number of events such as pain, headache, dizziness, or feeling faint, without serious unwanted effects.

However, the absence of reported adverse events does not necessarily demonstrate safety when studies have not systematically collected or reported them.

Immersive virtual reality can cause visual fatigue, disorientation, headache, or cybersickness. Robotic devices may produce discomfort, abnormal joint loading, skin irritation, or pain when they are poorly adjusted.

Safety procedures should include device calibration, ergonomic positioning, movement-range limits, supervision, emergency stopping mechanisms, monitoring for fatigue, and evaluation of pain or autonomic symptoms.

Portable and home-based systems may improve access to treatment, but they also transfer part of the responsibility for setup and monitoring to patients and caregivers. Remote supervision, secure data transmission, technical support, and clear eligibility criteria are necessary.

Outcome Selection and Functional Transfer

The outcome distribution showed that 90% of the evidence syntheses evaluated motor function, while 70% assessed activities of daily living, 30% evaluated quality of life or participation, 20% assessed safety, and only 10% directly evaluated neuroplasticity.

This pattern demonstrates a strong emphasis on impairment-based outcomes. Motor scales are important, but the final purpose of stroke rehabilitation is to improve independence, participation, and quality of life.

Future trials should include outcomes across the domains of the International Classification of Functioning, Disability and Health:

- Body functions and structures.
- Activities.
- Participation.
- Environmental factors.
- Personal factors.

Real-world arm use can be assessed through wearable sensors, activity monitors, ecological assessments, and patient-reported outcomes. These measures can help determine whether improvements observed in clinical or virtual environments persist in everyday life.

Functional transfer should not be assumed solely because patients improve their performance within a technological system.

Methodological Limitations of the Evidence

Several methodological limitations were identified. First, substantial heterogeneity existed in the devices, immersion levels, robotic mechanisms, feedback modalities, session duration, total dose, comparison groups, and outcome instruments.

This variability makes it difficult to determine which therapeutic component is responsible for the observed improvement.

Second, the systematic reviews and meta-analyses were generally constructed from small primary studies. The six quantitative syntheses analyzed in Figure 8 included approximately 32 to 48 participants per primary study.

Small trials may generate imprecise estimates and are more vulnerable to baseline imbalances, selective reporting, and exaggerated treatment effects.

Third, participant and therapist blinding is difficult in rehabilitation research. Patients and professionals usually know which intervention is being delivered, increasing the possibility of expectation and performance effects. Outcome assessors should therefore be blinded whenever possible.

Fourth, follow-up periods were frequently short. Immediate improvements cannot establish whether benefits persist or translate into long-term independence.

Fifth, several reviews may contain overlapping trials. Their pooled samples cannot be added because this could count the same participants more than once. Agreement among reviews may also partly reflect repeated analysis of the same primary evidence.

Limitations of the Present Review

The present study was an integrative synthesis of 20 selected high-quality publications rather than an exhaustive meta-analysis of every available clinical trial.

The thematic and directional classifications were developed for descriptive purposes and involved interpretive judgment. Different classification criteria could produce slight variations in the distribution of the findings.

Only English- and Spanish-language publications were considered, which may have excluded relevant evidence published in other languages.

Technological development also occurs rapidly. Newer systems may have different levels of immersion, movement detection, portability, feedback, and personalization than the devices evaluated in earlier studies.

A new pooled effect size was not calculated because of methodological heterogeneity and possible overlap among systematic reviews. Consequently, this study identifies patterns in the evidence but does not provide a single numerical estimate of the effectiveness of digital neurorehabilitation.

Evaluation of the Hypotheses

The principal hypothesis was partially supported. Virtual reality and robot-assisted rehabilitation were associated with improvements in selected motor, functional, and neuroplasticity-related outcomes.

The evidence was most favorable when the technology provided active, repetitive, intensive, task-specific, progressively challenging, and feedback-rich practice.

The hypothesis that digital technologies are more effective as complementary tools rather than universal replacements for conventional rehabilitation was also supported.

Several favorable results occurred when technology increased the total treatment dose. Dose-matched comparisons frequently showed smaller differences or equivalence with conventional therapy.

The third hypothesis was supported by the variability related to stroke stage, treatment duration, active participation, immersion level, robotic assistance, outcome selection, and follow-up.

The results indicate that effectiveness cannot be attributed solely to the presence of a virtual or robotic device.

CONCLUSIÓN

Virtual reality and robot-assisted rehabilitation represent relevant strategies for contemporary post-stroke neurorehabilitation. The evidence analyzed indicates that both technologies can increase treatment intensity, movement repetition, task specificity, feedback, and patient participation—elements directly associated with motor learning and experience-dependent neuroplasticity.

Virtual reality demonstrated generally favorable results in upper-limb motor function, dexterity, functional independence, and selected quality-of-life outcomes. It was also associated with changes in cortical activation and functional connectivity. Nevertheless, its effects varied according to immersion level, intervention duration, total treatment dose, time since stroke, and the characteristics of the comparison therapy.

Robot-assisted rehabilitation provided measurable and standardized training and showed benefits in motor control, muscle strength, and upper-limb performance. However, its superiority over dose-matched conventional rehabilitation was inconsistent. Improvements at the impairment level did not always translate into greater independence or spontaneous use of the affected limb in daily life. Robotic assistance should therefore preserve voluntary effort and be integrated with functional, meaningful, and progressively challenging activities.

The combination of virtual reality and robotics appears promising because it integrates physical assistance and haptic interaction with immersive environments, motivational elements, and multisensory feedback. However, the available evidence remains limited, and additional direct comparative trials are required before establishing its superiority over either technology alone.

The principal hypothesis was partially supported. Digital neurorehabilitation can promote motor and functional recovery, particularly when it provides active, repetitive, intensive, task-specific, and feedback-rich training. Nevertheless, technology alone does not guarantee adaptive neuroplasticity or clinically meaningful recovery. Its effectiveness depends on patient selection, treatment parameters, active participation, professional supervision, and transfer of training to real-world activities.

The evidence also demonstrates that statistical significance should not be interpreted automatically as clinical relevance. Small improvements in motor scales may not exceed clinically important thresholds or improve activities of daily living, participation, and quality of life. Future studies should report effect sizes, confidence intervals, minimal clinically important differences, adverse events, and long-term follow-up.

Current research remains limited by small primary samples, heterogeneous devices, differences in rehabilitation dose, short follow-up periods, and insufficient evaluation of neuroplasticity, safety, participation, and cost-effectiveness. Future randomized trials should use dose-matched control groups, standardized intervention descriptions, blinded outcome assessment, and combined clinical, neuroimaging, neurophysiological, and biological measurements.

In conclusion, virtual reality and robotic rehabilitation should be considered complementary components of comprehensive post-stroke care rather than universal replacements for physical or occupational therapy. Their greatest clinical value lies in expanding the quantity and quality of rehabilitation while maintaining individualized goals, therapist supervision, patient safety, and meaningful functional practice.

The future of digital neurorehabilitation will depend not only on developing more advanced devices, but also on identifying which technology, dose, timing, feedback modality, and level of assistance are most appropriate for each patient. A personalized and evidence-based approach is essential to transform technological performance into sustained independence and participation after stroke.

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