DISSERTATION

zur Erlangung des akademischen Grades doctor medicinae (Dr. med.)

Gamifying Rehab - The Effect of Reward-Oriented VR Games in Post-Stroke Patients

vorgelegt dem Rat der Medizinischen Fakultät

der Friedrich-Schiller-Universität Jena von

Valentin Wilkens

Jena, TT.MM.JJJJ

1 Inhaltsverzeichnis

2 Summary

3 Abstract

4 Introduction

Stroke remains one of the world's most consequential health problems. The World Stroke Organization (WSO) Global Stroke Fact Sheet 2025 reports stroke as the second leading cause of death globally and documents large rises since 1990 in incident strokes (+70%), deaths (+44%), and DALYs (+32%). It also estimates the global economic cost of stroke at > US \$890 billion annually (≈0.66% of global GDP) and projects a near doubling by 2050, underscoring mounting societal impact (Feigin et al., 2025). Beyond global figures, contemporary burden analyses of ischemic stroke show > 70 million DALYs in 2021, illustrating the scale of years of healthy life lost to stroke-related disability (Li et al., 2024). Complementing global data, AHA cardiovascular statistics emphasize the continuing mortality footprint in the U.S., where stroke remains a leading cause of death (Yao et al., 2021).

The disability consequences for survivors are profound and enduring. Community-based cohort work shows substantial long-term functional disability among stroke survivors, with persistent limitations in ADLs and mobility that carry important implications for independence and quality of life (Yao et al., 2021). Post-stroke mood disorders are highly prevalent: recent systematic reviews/meta-analyses estimate post-stroke depression (PSD) point prevalence ≈ 27–31% and post-stroke anxiety ≈ 39%, with early-onset depression (≤ 3 months) predicting persistence over the first year (Ignacio et al., 2024; Liu et al., 2023). These affective symptoms further undermine participation in therapy and recovery trajectories. The burden extends to families. Multiple systematic reviews document high and persistent caregiver burden and identify modifiable targets for caregiver-focused interventions that can reduce burden at follow-up in randomized trials, highlighting the dyadic nature of stroke rehabilitation (Bakas et al., 2022; Jammal et al., 2024; Tziaka et al., 2024). Economically, the costs accrue across acute care, inpatient/outpatient rehabilitation, and long-term support. A comprehensive systematic review of cost-of-illness studies reports substantial per-patient annual costs in high-income settings (e.g., US\$ 60k in the United States), reinforcing the need for cost-effective, disability-reducing interventions (Strilciuc et al., 2021).

Returning to work (RTW) is a critical patient-centered outcome that encapsulates functional, psychological, and economic recovery. Although figures vary by cohort and age, evidence syntheses and applied health reports commonly cite < 50% RTW at one year in unselected stroke populations, and methodological reviews call for stronger randomized evidence around RTW interventions (Chen et al., 2023; Trusson et al., 2025). Specific cohorts (e.g., young-adult ischemic stroke) achieve higher RTW rates, illustrating heterogeneity by age and baseline function but not diminishing the general challenge (Kwok et al., 2025).

The timing of rehabilitation is one of the strongest determinants of recovery after stroke. Experimental and clinical research converge on the existence of a time-limited phase of heightened neuroplasticity during which the injured brain exhibits exceptional capacity for reorganization. In foundational animal work, Biernaskie et al. showed that rats beginning rehabilitative training five days after focal ischemia achieved markedly greater improvements in skilled forelimb use and cortical reorganization than those trained thirty days post-lesion, establishing a temporal window of maximal responsiveness (Biernaskie et al., 2004). Subsequent primate and rodent studies confirmed that early task-specific training promotes axonal sprouting, dendritic growth, and synaptic strengthening in perilesional cortex, whereas delayed intervention yields blunted effects (Nudo et al., 2001). Human neurophysiological evidence mirrors these findings: motor-cortex excitability and inter-hemispheric rebalancing are transiently enhanced within the first three months after stroke, suggesting a biological "critical period" for recovery (Mang et al., 2013; Swayne et al., 2008). Together these studies indicate that recovery potential follows a biologically defined gradient of plasticity, peaking early and gradually declining thereafter.

This mechanistic rationale has been tested directly in clinical trials. The Critical Period After Stroke Study (CPASS)—a randomized controlled trial evaluating 20 hours of additional upper-limb therapy delivered at different post-stroke intervals—found that patients who began intensive training within 30 days achieved significantly greater improvements in Action Research Arm Test (ARAT) scores than those who started later (Edwardson et al., 2023). Supporting evidence from a 2023 systematic review and meta-analysis showed that initiating rehabilitation within the first two weeks led to superior outcomes on the Barthel Index and activities-of-daily-living measures compared with delayed programs (Wei et al., 2024). Functional-imaging studies likewise demonstrate stronger ipsilesional-hemisphere activation and re-establishment of corticospinal connectivity during this subacute phase (Ballester et al., 2019).

Still, "earlier" is not synonymous with "better." The AVERT trial, a multicenter RCT including over 2,000 participants, revealed that very early mobilization (< 24 hours) led to poorer functional outcomes at 3 months relative to standard care, likely because of hemodynamic instability and excessive exertion during acute infarct evolution (Bernhardt & Langhorne, 2015). Subsequent pilot RCTs in patients following mechanical thrombectomy found early mobilization to be feasible and to enhance daily-activity scores, but only when the dose and timing were carefully individualized (Wang et al., 2022). These findings emphasize the need for judicious calibration of both onset and intensity of therapy in the days immediately following stroke.

Overall, converging mechanistic, neurophysiological, and randomized evidence defines a critical subacute window, from several days to roughly three months post-stroke, during which the nervous system is most receptive to rehabilitative experience. Delivering high-quality, engaging motor training within this window can produce disproportionately large and durable functional gains. Yet, logistical barriers often limit early therapy in hospital settings,

particularly when patients are medically fragile. This gap underscores the importance of accessible, portable interventions that can be implemented directly at the bedside to exploit this sensitive period—an opportunity that virtual-reality-based rehabilitation uniquely provides.

Virtual reality (VR) has emerged as a promising adjunct to conventional stroke rehabilitation, offering a means to deliver intensive, task-specific, and engaging training during the critical post-stroke period. The approach leverages immersive, interactive environments to simulate real-world movements and provide multisensory feedback that enhances motor relearning. By combining visual, auditory, and haptic cues, VR allows patients to perform repetitive goal-directed tasks in motivating contexts that encourage sustained participation—an essential feature given that neuroplasticity is activity-dependent.

A rapidly growing evidence base supports the clinical utility of VR in stroke recovery. A 2024 systematic review and meta-analysis of randomized controlled trials concluded that immersive and non-immersive VR interventions significantly improved Fugl-Meyer Assessment–Upper Extremity (FMA-UE) and Box and Block Test (BBT) scores compared to conventional therapy, with pooled standardized mean differences in the moderate range (Kenea et al., 2025). Similarly, a 2025 network meta-analysis including 20 RCTs found that VR-based therapy improved upper-limb motor function and activities of daily living, with non-immersive and semi-immersive modalities (e.g., Kinect-based systems) showing the largest effect sizes (Zhang et al., 2025). These findings are consistent with earlier umbrella reviews showing that VR-enhanced interventions outperform standard care in improving motor recovery, balance, and self-efficacy across both acute and chronic phases of stroke (Wu & Pang, 2025). Notably, several of these analyses reported that VR's benefits extend beyond motor outcomes, contributing to greater patient motivation and adherence to therapy schedules.

At the mechanism level, neuroimaging and electrophysiology show that VR-based training engages—and can reorganize—motor networks. An open-access randomized controlled trial in subacute stroke used resting-state fMRI and showed that immersive VR (imVR) plus standard care produced greater upper-limb improvements, accompanied by connectivity changes in ipsilesional premotor/dorsolateral prefrontal cortex acutely, and visual–frontoparietal regions at 12-week follow-up (connectivity changes correlated with motor gains) (Huang et al., 2024). Earlier work in stroke with task fMRI reported cortical reorganization associated with functional recovery after VR interventions, supporting the plausibility of VR-induced plasticity in humans (Jang et al., 2005; You et al., 2005). Complementing MRI, EEG studies demonstrate VR-linked mu-rhythm desynchronization/coherence changes in bilateral M1 and parietal cortices during immersive VR mirror-visual-feedback tasks in stroke, consistent with sensorimotor engagement and corticospinal reweighting; related randomized work shows VR-enhanced spectral perturbations and improved motor performance (Calabrò et al., 2017; Chang et al., 2023). Recent reviews bridge these literatures, summarizing fMRI/EEG evidence that VR

protocols modulate primary motor circuits and connectivity relevant to motor relearning (Arcuri et al., 2021; Feitosa et al., 2022).

Despite these advantages, conventional PC-tethered VR systems have faced notable practical barriers. They are typically bulky, expensive, and immobile, requiring powerful external computers, wired headsets, and dedicated clinical spaces. A systematic review on practical barriers in home- and clinic-based virtual rehabilitation identified hardware weight, cybersickness, high cost, and space constraints as the most frequent limitations (Threapleton et al., 2016). These issues have historically restricted the use of immersive VR to specialized research settings rather than routine clinical care. As a result, many stroke patients—particularly those in the early, medically fragile stage—are unable to access such therapies during the optimal window for plasticity.

The recent advent of standalone, portable head-mounted displays (HMDs) has the potential to overcome these logistical hurdles. Devices such as the Meta Quest 3 integrate all computational components within the headset, eliminating external cabling and enabling use directly at the bedside. Modern HMDs are lightweight (≈500 g), self-contained, and increasingly affordable, allowing deployment even in resource-limited environments. Reviews on head-mounted VR systems in physical rehabilitation emphasize their feasibility, improved comfort, and adaptability across clinical contexts, including inpatient stroke units (Saldana et al., 2020). This technological shift transforms VR from a laboratory-bound tool into a scalable and bedside-accessible intervention, capable of delivering high-dose, engaging motor therapy during the critical subacute phase.

Collectively, the literature demonstrates that VR-based rehabilitation effectively complements traditional physiotherapy by enhancing feedback, motivation, and training intensity. However, most existing systems remain underutilized in early post-stroke care due to their technical complexity and lack of portability. Bridging this gap requires VR solutions that are simple, autonomous, and deployable directly on the stroke unit—qualities that define the next generation of portable, all-in-one VR interventions. HMD technology is evolving constantly and so is the versatility of application. Crucially, though, rehabilitation should harness this technology's potential to enable highly motivating experiences.

Motivational reinforcement is a powerful driver of motor learning and plasticity, with dopamine acting as a key neuromodulator that encodes reward-prediction errors (the difference between expected and received outcomes) to strengthen actions that lead to desired results. Contemporary reviews synthesize convergent animal and human evidence that midbrain dopaminergic neurons broadcast these teaching signals to cortico-striato-thalamo-cortical loops, shaping habit formation and motor skill acquisition—precisely the circuits we try to recruit in post-stroke training (Lerner et al., 2021; Nasser et al., 2017; Wood, 2021).

Stroke can blunt this reinforcement machinery. A 2023 clinical study found reward-network dysfunction in the acute phase associated with worse cognitive performance, suggesting a reduced capacity to use reward for learning unless therapy explicitly and repeatedly engages these systems. This provides a mechanistic rationale for embedding rich, contingent reward into rehabilitation to compensate for early network inefficiencies (Wagner et al., 2023).

Clinical trials support the therapeutic value of reward. In an assessor-blinded, multicenter randomized controlled trial, Widmer and colleagues compared reward-enhanced arm training with control feedback in stroke survivors (Widmer et al., 2022a). While the primary endpoint was neutral, the rewarded group showed greater training-mediated improvements in impairment and activity measures—evidence that explicit reward augments the gains achievable from the same motor practice "dose" (Widmer et al., 2022a). Beyond impairment-oriented outcomes, reward also shapes how people learn and retain skills. In a seminal human study, Galea et al. (2015) showed a double dissociation: punishment accelerates the speed of adaptation, whereas reward selectively enhances retention—the ability to keep improvements when guidance is withdrawn. This matters in rehab because durable carry-over into daily life is a primary goal (Galea et al., 2015).

Crucially, this pattern generalizes to stroke. A 2024 acute-stroke trial tested reinforcement signals during paretic-hand sensorimotor adaptation: reward feedback enhanced both initial learning and retention, while punishment hindered recovery—strongly arguing for reward-heavy (not punishment-heavy) designs early after stroke. These results align tightly with the Galea dissociation and point to concrete design choices for therapy (Paul et al., 2024).

Taken together, the mechanism-to-trial chain is clear: dopamine-mediated reward signals teach the nervous system which actions to reinforce; stroke can impair this circuitry, increasing the need for salient, well-timed rewards; RCT and adaptation studies show that adding reward to identical motor practice yields bigger and more durable gains, whereas punishment may be counterproductive. For this dissertation's intervention, that translates into VR tasks with immediate, contingent, and escalating rewards (points, streaks, progress cues, haptics, celebratory feedback), calibrated to emphasize retention and transfer rather than mere short-term speedups—leveraging neuroscience to turn practice into lasting function.

5 Objectives

The present study aimed to evaluate the effects of a custom VR-based intervention on upper-limb rehabilitation in post-stroke patients. The objectives were defined as follows:

Primary Objective:

To investigate whether the addition of the VR intervention to conventional training improves upper-limb motor performance, as measured by the Serial Reaction Time (SRT) task and standardized motor assessments, compared to conventional training alone.

Secondary Objective:

To examine whether VR training influences patient motivation and engagement during rehabilitation sessions, assessed via the Motivation in Patients for Rehabilitation Scale (MORE).

Exploratory Objective:

To explore potential relationships between baseline characteristics (e.g., apathy scores, prior gaming experience, age) and responsiveness to the VR intervention, in order to identify factors that may predict individual benefit from VR-based rehabilitation.

6 Materials and Methods

6.1 Participants

43 Patients between the ages of 54 and 85 were included in this study. 6 additional participants were excluded due to stroke severity (4), cognitive impairment (1) or inability to perform tasks (1). 4 female and 18 male patients with first-ever acute ischemia in the supply area of the MCA made up the non-VR group, with 8 female and 13 male patients present in the VR-group. Stroke patterns were verified with a routine cMRT on admission and qualifying patients were assessed directly on the stroke unit after diagnosis in the first 1-6 days after stroke onset.

Participants were excluded based on the following criteria: depression, signs of dementia (MoCa < 20), Aphasia, Apraxia, loss of visual acuity and severe motion sickness. Prior to the examination, all participants were fully briefed on the experimental procedure. Informed consent was obtained from each subject before participation. The study received approval from the Ethics Committee of the University Hospital Jena (registration number: 2024-3598-BO-A).

6.2 Assessment

A range of standardized tests and questionnaires listed below were used to evaluate the fitness of the participants.

We employed the short, six-item version of the Fugl-Meyer-Assessment (Hsieh et al., 2007) to assess the severity of the upper-limb impairment with a maximum score of 12 points per side in addition to the Institutes of Health Stroke Scale (NIHSS). All participants demonstrated good upper limb motor function (upper limb NIHSS < 2). The participants' cognitive function was evaluated using the Montreal Cognitive Assessment (MoCa) and depression screening was performed with the short form of the Geriatric Depression Scale (GDS). Patients were also subject to a questionnaire querying age, sex, weight and height as well as drug consumption, their relationship with gambling and experience with computer gaming. Additionally, to rule out potential mood disorders, the Apathy Evaluation Scale (AES) was conducted. Patients were also asked to evaluate their motivation for rehabilitation at the end of the second and final day of intervention using the Motivation in Patients for Rehabilitation Scale (MORE).

6.3 Equipment and software

The custom VR-Game used in our study was developed on Windows 11 for the Meta Quest 3 using Unreal Engine 5 Version 5.3.1 with both free and paid assets from the Unreal Engine Marketplace. Game mechanics were developed with intermittent interdisciplinary feedback from ergo- and physiotherapists as well as patient feedback in a 2-week trial phase prior to the study.

6.4 Study design and procedure

The study employed a prospective, randomized, controlled two-group design. A block randomization list for 42 patients was generated using a custom Python script. On the first day of the intervention, each patient was assigned to a group by randomly drawing a number from this list. All participants underwent two consecutive days of intervention on the stroke unit. Each patient received one daily training session of 45 minutes. Both groups performed the standardized SRT (Serial Reaction Time Task) game. In addition, patients in the VR group completed the custom-developed VR game, whereas the control group received only the SRT in addition to standard therapy. Sessions were conducted under the supervision of the study investigator. Short breaks were permitted in case of fatigue, and sessions were discontinued in the event of dizziness, nausea, or lack of compliance.

6.5 Intervention

Both groups received two consecutive days of training on the stroke unit, with one 45-minute session per day. All participants completed the standardized Serial Reaction Time (SRT) task, which served as the baseline motor training intervention. In addition, the VR group received training with the custom-developed VR game designed to promote upper-limb motor activity and engagement through playful interaction. The game required patients to perform reaching, grasping, and coordination tasks in a virtual environment, providing immediate multisensory feedback. The game consisted of three consecutive tasks: the first task involved reaching and grasping for cubes to stack them on top of each other in a pre-defined order. The second task required patients to grab a ball and throw it through a ring moving in a 2-dimensional plane in front of them. Lastly, patients were asked to slice fruit with a katana. Difficulty levels could be adjusted according to patient ability. The control group completed only the SRT during the same period. All sessions were carried out on the stroke unit under the continuous supervision of the study investigator to ensure adherence to the protocol and participant safety. Short breaks were permitted in case of fatigue, and sessions were discontinued in the event of dizziness, nausea, or lack of compliance.

6.6 Serial Reaction Time Task (SRT)

To assess motor learning performance, all participants completed a shortened version of the Serial Reaction Time (SRT) task. The paradigm was programmed to consist of 120 blocks in total, subdivided into three conditions: 60 blue blocks (repeating sequence trials), 30 green blocks (repeating sequence trials), and 30 yellow blocks (random sequence trials).

Each block presented a series of 8 numerical stimuli (1–4) on the screen, with the numbers corresponding to spatially mapped keys on a gamepad. Participants were instructed to respond as quickly and accurately as possible by pressing the corresponding button with the dominant hand. Reaction time (RT, in milliseconds) was recorded for each stimulus. The task structure allowed differentiation between performance in structured (blue and green) versus unstructured (yellow) conditions. The repeating sequences (blue and green) were designed to elicit sequence-specific learning through repeated exposure, while the random sequences (yellow) controlled for general motor and attentional performance. Sequence learning was operationalized as a greater reduction in RT across repeating blocks compared to random blocks. All participants completed the SRT on both intervention days. Accuracy and RTs were automatically logged by the software for subsequent analysis. We employed a shortened version of the standard SRT (120 instead of 160 blocks), as pilot testing indicated that stroke patients were unable to successfully complete the longer version due to fatigue and attentional limitations. The adapted version maintained the core features of the paradigm - repeated structured sequences interleaved with random sequences - while ensuring feasibility and participant compliance.

6.7 VR Game implementation

The virtual reality game was developed in *Unreal Engine 5.3.1* (Epic Games) for the Meta Quest 3 using a combination of Blueprints and C++ programming together with the Meta OpenXR SDK to ensure hardware compatibility and responsive interaction. The game consisted of three consecutive tasks designed to address different domains of upper-limb motor rehabilitation. In the first task, participants stacked cubes in a predefined order, training reaching and grasping precision. In the second task, they grasped and threw a ball through a ring moving along a two-dimensional plane, thereby promoting controlled force application and hand–eye coordination. The final task required slicing moving fruit with a virtual katana. This level included a high-score display to enhance motivation and reward effort through playful competition.

A multimodal feedback system was integrated into all tasks. Haptic cues were delivered upon successful grasping and releasing of objects as well as when slicing fruit, while auditory feedback included naturalistic sounds such as a cluttering noise when objects fell to the ground or a slashing sound during fruit slicing. Task completion was marked by distinct confirmation tones. Visual feedback complemented these modalities through the highlighting of interacted

objects and the display of scores. To further improve compliance and reduce frustration with unfamiliar game mechanics, each level was narrated by the investigator, providing real-time instructions and encouragement throughout the session.

The game underwent a two-week beta testing phase with therapists and patients, during which several modifications were implemented to sustain motivation and minimize frustration. These included the addition of aiming assistance in the throwing task, automatic repositioning of dropped objects to their original location, and fine-tuning of difficulty levels to match individual motor abilities. These iterative adjustments ensured both feasibility and high patient engagement.

7 Results

A total of 43 patients were enrolled and completed the study procedures. During data preprocessing, SRT recordings were screened according to predefined quality criteria. Sessions were excluded in cases of incomplete recordings, implausibly short task durations, inconsistent session files across days, or extreme outlying performance trajectories. In addition, participants with markedly elevated apathy scores (AES > 40) were excluded to avoid undue influence of severe motivational impairment on task performance. After application of these criteria, data from N = 34 patients were included in the final analysis, comprising [VR: n = 20; control: n = 14]. All included participants completed both intervention days and contributed valid observations to the learning analyses.

Baseline demographic and clinical characteristics of the included participants are summarized in **Table 1**. The VR and non-VR groups were comparable with respect to age, sex distribution, educational level, and body mass index. No statistically significant differences were observed between groups at baseline.

Characteristic	VR group (n = 20)	Non-VR group (n = 14)	Total (n = 34)	p value
Age, years	66.2 ± 14.2	65.4 ± 7.7	65.8 ± 11.8	0.850
Range	20–84	54–76	20–84	
Sex				0.209
– Female	4 (20.0%)	6 (42.9%)	10 (29.4%)	
– Male	16 (80.0%)	8 (57.1%)	24 (70.6%)	
Education				0.317
– Apprenticeship	6 (30.0%)	6 (42.9%)	12 (35.3%)	
– University degree	8 (40.0%)	4 (28.6%)	12 (35.3%)	
Body mass index, kg/m²	26.6 ± 3.4	26.1 ± 4.8	26.4 ± 4.0	0.707

14

.

8 Discussion

9 Conclusion

10 Literaturverzeichnis

Arcuri, F., Porcaro, C., Ciancarelli, I., Tonin, P., & Cerasa, A. (2021). Electrophysiological Corre-

    lates of Virtual-Reality Applications in the Rehabilitation Setting: New Perspectives for

    Stroke Patients. *Electronics*, *10*(7), 836. https://doi.org/10.3390/electronics10070836

Bakas, T., McCarthy, M. J., & Miller, E. L. (2022). Systematic Review of the Evidence for Stroke

    Family Caregiver and Dyad Interventions. *Stroke*, *53*(6), 2093–2102.

    https://doi.org/10.1161/STROKEAHA.121.034090

Ballester, B. R., Maier, M., Duff, A., Cameirão, M., Bermúdez, S., Duarte, E., Cuxart, A.,

    Rodríguez, S., San Segundo Mozo, R. M., & Verschure, P. F. M. J. (2019). A critical time

    window for recovery extends beyond one-year post-stroke. *Journal of Neurophysiology*,

    122(1), 350–357. https://doi.org/10.1152/jn.00762.2018

Bernhardt, J., & Langhorne, P. (2015). Efficacy and safety of very early mobilisation within 24 h

    of stroke onset (AVERT): A randomised controlled trial. *The Lancet*, *386*(9988), 46–55.

    https://doi.org/10.1016/S0140-6736(15)60690-0

Biernaskie, J., Chernenko, G., & Corbett, D. (2004). Efficacy of rehabilitative experience de-

    clines with time after focal ischemic brain injury. *The Journal of Neuroscience: The Offi-*

    cial Journal of the Society for Neuroscience, *24*(5), 1245–1254.

    https://doi.org/10.1523/JNEUROSCI.3834-03.2004

Calabrò, R. S., Naro, A., Russo, M., Leo, A., De Luca, R., Balletta, T., Buda, A., La Rosa, G., Bra-

    manti, A., & Bramanti, P. (2017). The role of virtual reality in improving motor

performance as revealed by EEG: A randomized clinical trial. *Journal of Neuroengineering and Rehabilitation*, *14*(1), 53. https://doi.org/10.1186/s12984-017-0268-4

Chang, W. K., Lim, H., Park, S. H., Lim, C., Paik, N.-J., Kim, W.-S., & Ku, J. (2023). Effect of immersive virtual mirror visual feedback on Mu suppression and coherence in motor and parietal cortex in stroke. *Scientific Reports*, *13*(1), 12514. https://doi.org/10.1038/s41598-023-38749-8

Chen, N. Y. C., Dong, Y., & Kua, Z. Z. J. (2023). Addressing mood and fatigue in return-to-work programmes after stroke: A systematic review. *Frontiers in Neurology*, *14*. https://doi.org/10.3389/fneur.2023.1145705

Edwardson, M. A., Brady, K., Giannetti, M. L., Geed, S., Barth, J., Mitchell, A., Tan, M. T., Zhou, Y., Bregman, B. S., Newport, E. L., Edwards, D. F., & Dromerick, A. W. (2023). Interpreting the CPASS Trial: Do Not Shift Motor Therapy to the Subacute Phase. *Neurorehabilitation and Neural Repair*, *37*(1), 76–79. https://doi.org/10.1177/15459683221143461

Feigin, V. L., Brainin, M., Norrving, B., Martins, S. O., Pandian, J., Lindsay, P., F Grupper, M., & Rautalin, I. (2025). World Stroke Organization: Global Stroke Fact Sheet 2025. *International Journal of Stroke*, *20*(2), 132–144. https://doi.org/10.1177/17474930241308142

Feitosa, J. A., Fernandes, C. A., Casseb, R. F., & Castellano, G. (2022). Effects of virtual reality-based motor rehabilitation: A systematic review of fMRI studies. *Journal of Neural Engineering, 19*(1). https://doi.org/10.1088/1741-2552/ac456e

Galea, J. M., Mallia, E., Rothwell, J., & Diedrichsen, J. (2015). The dissociable effects of punishment and reward on motor learning. *Nature Neuroscience*, *18*(4), 597–602. https://doi.org/10.1038/nn.3956

Hsieh, Y.-W., Hsueh, I.-P., Chou, Y.-T., Sheu, C.-F., Hsieh, C.-L., & Kwakkel, G. (2007). Development and validation of a short form of the Fugl-Meyer motor scale in patients with stroke. *Stroke*, *38*(11), 3052–3054. https://doi.org/10.1161/STROKEAHA.107.490730

Huang, Q., Jiang, X., Jin, Y., Wu, B., Vigotsky, A. D., Fan, L., Gu, P., Tu, W., Huang, L., & Jiang, S. (2024). Immersive virtual reality-based rehabilitation for subacute stroke: A randomized controlled trial. *Journal of Neurology*, *271*(3), 1256–1266. https://doi.org/10.1007/s00415-023-12060-y

Ignacio, K. H. D., Muir, R. T., Diestro, J. D. B., Singh, N., Yu, M. H. L. L., Omari, O. E., Abdalrahman, R., Barker-Collo, S. L., Hackett, M. L., Dukelow, S. P., & Almekhlafi, M. A. (2024). Prevalence of depression and anxiety symptoms after stroke in young adults: A systematic review and meta-analysis. *Journal of Stroke and Cerebrovascular Diseases: The Official Journal of National Stroke Association*, *33*(7), 107732. https://doi.org/10.1016/j.jstrokecerebrovasdis.2024.107732

Jammal, M., Kolt, G. S., Liu, K. P. Y., Guagliano, J. M., Dennaoui, N., & George, E. S. (2024). A systematic review and meta-analysis of randomized controlled trials to reduce burden, stress, and strain in informal stroke caregivers. *Clinical Rehabilitation*, *38*(11), 1429–1445. https://doi.org/10.1177/02692155241271047

Jang, S. H., You, S. H., Hallett, M., Cho, Y. W., Park, C.-M., Cho, S.-H., Lee, H.-Y., & Kim, T.-H. (2005). Cortical reorganization and associated functional motor recovery after virtual reality in patients with chronic stroke: An experimenter-blind preliminary study. *Archives of Physical Medicine and Rehabilitation*, *86*(11), 2218–2223. https://doi.org/10.1016/j.apmr.2005.04.015

Jeanne Funk Brockmyer, Brockmyer, J. H., Christine Fox, Fox, C. M., Kathleen Curtiss, Curtiss,

    K., Evan McBroom, McBroom, E., Kimberly Burkhart, Burkhart, K., Jacquelyn N.

    Pidruzny, & Pidruzny, J. N. (2009). The development of the Game Engagement Ques-

    tionnaire: A measure of engagement in video game-playing. *Journal of Experimental*

    Social Psychology, *45*(4), 624–634. https://doi.org/10.1016/j.jesp.2009.02.016

Kenea, C. D., Abessa, T. G., Lamba, D., & Bonnechère, B. (2025). Immersive Virtual Reality in

    Stroke Rehabilitation: A Systematic Review and Meta-Analysis of Its Efficacy in Upper

    Limb Recovery. *Journal of Clinical Medicine*, *14*(6), 1783.

    https://doi.org/10.3390/jcm14061783

Kwok, G. Y. R., Yeong, N., Law, M., Kang, Z. L., Achar, A., Lim, X. Y., Ng, M. B. J., Teo, Y., Tan, S.

    M. L., Ho, J. S. Y., Marmin, M., Hassan, F., Chia, M. L. J., Wong, L. Y. H., Sia, C., Sharma,

    V. K., Yeo, L. L. L., Ahmad, A., & Tan, B. Y. Q. (2025). Return to Work After Ischemic

    Stroke in Young Adults: A Multicenter Cohort Study, Systematic Review, and Meta-

    Analysis. *Journal of the American Heart Association*, *14*(8), e036427.

    https://doi.org/10.1161/JAHA.124.036427

Lerner, T. N., Holloway, A. L., & Seiler, J. L. (2021). Dopamine, Updated: Reward Prediction Er-

    ror and Beyond. *Current opinion in neurobiology*, *67*, 123–130.

    https://doi.org/10.1016/j.conb.2020.10.012

Li, X., Kong, X., Yang, C., Cheng, Z., Lv, J., Guo, H., & Liu, X. (2024). Global, regional, and na-

    tional burden of ischemic stroke, 1990–2021: An analysis of data from the global bur-

    den of disease study 2021. *eClinicalMedicine*, *75*.

    https://doi.org/10.1016/j.eclinm.2024.102758

Liu, L., Xu, M., Marshall, I. J., Wolfe, C. D., Wang, Y., & O'Connell, M. D. (2023). Prevalence and natural history of depression after stroke: A systematic review and meta-analysis of observational studies. *PLoS Medicine*, *20*(3), e1004200. https://doi.org/10.1371/journal.pmed.1004200

Mang, C. S., Campbell, K. L., Ross, C. J. D., & Boyd, L. A. (2013). Promoting neuroplasticity for motor rehabilitation after stroke: Considering the effects of aerobic exercise and genetic variation on brain-derived neurotrophic factor. *Physical Therapy*, *93*(12), 1707–1716. https://doi.org/10.2522/ptj.20130053

Nasser, H. M., Calu, D. J., Schoenbaum, G., & Sharpe, M. J. (2017). The Dopamine Prediction Error: Contributions to Associative Models of Reward Learning. *Frontiers in Psychology*, *8*. https://doi.org/10.3389/fpsyg.2017.00244

Nudo, R. J., Plautz, E. J., & Frost, S. B. (2001). Role of adaptive plasticity in recovery of function after damage to motor cortex. *Muscle & Nerve*, *24*(8), 1000–1019. https://doi.org/10.1002/mus.1104

Paul, T., Wiemer, V. M., Günther, J., Lehnberg, F. M., Grafton, S. T., Fink, G. R., & Volz, L. J. (2024). *Reward enhances motor adaptation learning in acute stroke patients* (S. 2024.04.03.24305243). medRxiv. https://doi.org/10.1101/2024.04.03.24305243

Saldana, D., Neureither, M., Schmiesing, A., Jahng, E., Kysh, L., Roll, S. C., & Liew, S.-L. (2020). Applications of Head-Mounted Displays for Virtual Reality in Adult Physical Rehabilitation: A Scoping Review. *The American Journal of Occupational Therapy*, *74*(5), 7405205060p1-7405205060p15. https://doi.org/10.5014/ajot.2020.041442

Strilciuc, S., Grad, D. A., Radu, C., Chira, D., Stan, A., Ungureanu, M., Gheorghe, A., & Muresanu, F.-D. (2021). The economic burden of stroke: A systematic review of cost of

illness studies. *Journal of Medicine and Life*, *14*(5), 606–619.

https://doi.org/10.25122/jml-2021-0361

Swayne, O. B. C., Rothwell, J. C., Ward, N. S., & Greenwood, R. J. (2008). Stages of motor output reorganization after hemispheric stroke suggested by longitudinal studies of cortical physiology. *Cerebral Cortex (New York, N.Y.: 1991)*, *18*(8), 1909–1922.

https://doi.org/10.1093/cercor/bhm218

Threapleton, K., Drummond, A., & Standen, P. (2016). Virtual rehabilitation: What are the practical barriers for home-based research? *Digital health*, *2*, 2055207616641302.

https://doi.org/10.1177/2055207616641302

Trusson, D., Powers, K., Radford, K., Bowen, A., Craven, K., Holmes, J., Lindley, R., McKevitt, C., Phillips, J., Thompson, E., Watkins, C., Clarke, D. J., Trusson, D., Powers, K., Radford, K., Bowen, A., Craven, K., Holmes, J., Lindley, R., … Clarke, D. J. (2025). *Experiences of support to return to work after stroke: Longitudinal case studies from RETAKE trial*. National Institute for Health and Care Research.

Tziaka, E., Tsiakiri, A., Vlotinou, P., Christidi, F., Tsiptsios, D., Aggelousis, N., Vadikolias, K., & Serdari, A. (2024). A Holistic Approach to Expressing the Burden of Caregivers for Stroke Survivors: A Systematic Review. *Healthcare*, *12*(5), 565.

https://doi.org/10.3390/healthcare12050565

Wagner, F., Rogenz, J., Opitz, L., Maas, J., Schmidt, A., Brodoehl, S., Ullsperger, M., & Klingner, C. M. (2023). Reward network dysfunction is associated with cognitive impairment after stroke. *NeuroImage. Clinical*, *39*, 103446.

https://doi.org/10.1016/j.nicl.2023.103446

Wang, W., Wei, M., Cheng, Y., Zhao, H., Du, H., Hou, W., Yu, Y., Zhu, Z., Qiu, L., Zhang, T., & Wu, J. (2022). Safety and Efficacy of Early Rehabilitation After Stroke Using Mechanical Thrombectomy: A Pilot Randomized Controlled Trial. *Frontiers in Neurology*, *13*. https://doi.org/10.3389/fneur.2022.698439

Wei, X., Sun, S., Zhang, M., & Zhao, Z. (2024). A systematic review and meta-analysis of clinical efficacy of early and late rehabilitation interventions for ischemic stroke. *BMC Neurology*, *24*, 91. https://doi.org/10.1186/s12883-024-03565-8

Widmer, M., Held, J. P. O., Wittmann, F., Valladares, B., Lambercy, O., Sturzenegger, C., Palla, A., Lutz, K., & Luft, A. R. (2022a). Reward During Arm Training Improves Impairment and Activity After Stroke: A Randomized Controlled Trial. *Neurorehabilitation and Neural Repair*, *36*(2), 140–150. https://doi.org/10.1177/15459683211062898

Widmer, M., Held, J. P. O., Wittmann, F., Valladares, B., Lambercy, O., Sturzenegger, C., Palla, A., Lutz, K., & Luft, A. R. (2022b). Reward During Arm Training Improves Impairment and Activity After Stroke: A Randomized Controlled Trial. *Neurorehabilitation and Neural Repair*, *36*(2), 140–150. https://doi.org/10.1177/15459683211062898

Wood, A. N. (2021). New roles for dopamine in motor skill acquisition: Lessons from primates, rodents, and songbirds. *Journal of Neurophysiology*, *125*(6), 2361–2374. https://doi.org/10.1152/jn.00648.2020

Wu, X., & Pang, W. (2025). Meta-analysis on the impact of virtual reality technology on limb function and quality of life in stroke patients—Application of virtual reality technology in rehabilitation training of stroke patients. 21(7), 51–61. https://doi.org/10.22514/sv.2025.096

Yao, Y.-Y., Wei, Z.-J., Zhang, Y.-C., Li, X., Gong, L., Zhou, J.-W., Wang, Y., Zhang, Y.-Y., & Wang, R.-P. (2021). Functional Disability After Ischemic Stroke: A Community-Based Cross-Sectional Study in Shanghai, China. *Frontiers in Neurology*, *12*, 649088. https://doi.org/10.3389/fneur.2021.649088

You, S. H., Jang, S. H., Kim, Y.-H., Hallett, M., Ahn, S. H., Kwon, Y.-H., Kim, J. H., & Lee, M. Y. (2005). Virtual Reality–Induced Cortical Reorganization and Associated Locomotor Recovery in Chronic Stroke: An Experimenter-Blind Randomized Study. *Stroke*, *36*(6), 1166–1171. https://doi.org/10.1161/01.STR.0000162715.43417.91

Zhang, J., Liu, M., Yue, J., Yang, J., Xiao, Y., Yang, J., & Cai, E. (2025). Effects of virtual reality with different modalities on upper limb recovery: A systematic review and network meta-analysis on optimizing stroke rehabilitation. *Frontiers in Neurology*, *16*. https://doi.org/10.3389/fneur.2025.1544135