Neuropsychology

ISSN: 3035-062X
2026, 3 (1)

Preliminary Reports and Negative Results in Life Science and Humanities

"Exploring VESPA 2.0 Implementation for Cognitive Rehabilitation in Severe Acquired Brain Injury: A Preliminary Study"

Davide Cardile[*1,2], Francesco Corallo[1], Helena Danesvalle[2], Daniele Mollaioli[2], Salvatore Marco Pappalardo[3], Noemi Giovinco[2], Rosalia Calapai[1], Miriana Mirabile[1], Rosaria De Luca[1], Maria Grazia Maggio[1], Desiree Latella[1], Carmela Rifici[1], Angelo Quartarone.[1], Laura Culicetto[1], Francesco Tomaiuolo[2], and Rocco Salvatore Calabrò[1]

[1] Centro Neurolesi "Bonino-Pulejo", 98124, Messina, Italy;
[2] Department of Clinical and Experimental Medicine, University of Messina, Piazza Pugliatti, 1, 98122 Messina, Italy;
[3] Software Engineering Italia S.r.l., Via Santa Sofia, Catania, Italy
Corresponding Author: davide.cardile@irccsme.it

Section: Neuropsychology

Citation: Cardile, D., Corallo, F., Danesvalle, H., Mollaioli, D., Pappalardo, S. M., Giovinco, N., Calapai, R., Mirabile, A., De Luca, R., Maggio, M. G., Latella, D., Rifici, C., Quartarone, A., Culicetto, L., Tomaiuolo, F., & Calabrò, R. S. (2026). Exploring VESPA 2.0 Implementation for Cognitive Rehabilitation in Severe Acquired Brain Injury: A Preliminary Study. *Preliminary Reports and Negative Results in Life Science and Humanities.* 3 (1), ISSN: 3035-062X DOI**:** https://doi.org/10.13129/3035-062X/prnr-5542

Abstract

Background: Severe acquired brain injury (ABI) frequently results in profound cognitive impairment. Non-immersive virtual reality (VR) delivered at the bedside represents a promising rehabilitation tool for patients who have emerged from a minimally conscious state.

Objective: To evaluate the feasibility, safety, and preliminary efficacy of VESPA 2.0, a tablet-based non-immersive VR system, for cognitive rehabilitation in severe ABI.

Methods: Six patients (4 males, 2 females; mean age 40.8 ± 14.5 years) with traumatic brain injury (n = 1), ischemic stroke (n = 4), or cerebral hemorrhage (n = 1) completed a 12-week individualized bedside VR training program (30–45 min, three times/week), targeting orientation, attention, reaction time, semantic memory, and executive functions. Clinical outcomes (MMSE, FIM, Barthel Index, RCS-E) were assessed at baseline, mid-treatment, and post-treatment. Group-level changes were examined via Friedman tests; individual task trajectories were analyzed using Kendall's Tau-U.

Results: All patients completed the protocol with full adherence and no adverse events. Significant group-level improvements were observed in MMSE ($\chi^2(2) = 11.273$, $p = .004$, $W = 0.939$), FIM ($\chi^2(2) =$

ISSN: 3035-062X
2026, 3 (1)

Preliminary Reports and Negative Results in Life Science and Humanities

10.333, p = .006, W = 0.861), and Barthel Index ($\chi^2(2) = 10.000$, p = .007, W = 0.833), all with large effect sizes. At the single-case level, two patients achieved statistically significant Tau-U effects: the patient with TBI showed faster semantic matching performance (Tau-U = −0.97, p < .05), and one patient with ischemic stroke reached maximal accuracy in semantic categorization (Tau-U = +1.00, p < .05). Remaining patients showed positive but non-significant trends. All patients preferred VR over traditional paper-and-pencil exercises.

Conclusions: Tablet-based, bedside non-immersive VR with VESPA 2.0 was feasible, safe, and associated with significant cognitive and functional gains in severe ABI. Larger controlled trials are warranted to confirm these preliminary findings.

Keywords: acquired brain injury, virtual reality, neurorehabilitation, cognitive recovery, neuroplasticity

Introduction

Severe acquired brain injury (ABI) is defined as a brain insult resulting in coma lasting more than 24 hours and long-term disability. It represents one of the major causes of death and chronic disability worldwide, with incidence rates ranging from 40 to 100 cases per 100,000 inhabitants annually [World Health Organization, 2006; Tagliaferri et al., 2006]. After emergence from Minimally Conscious State (EMCS), deficits in attention, memory, and executive functions remain among the most disabling sequelae, limiting rehabilitation potential and reintegration into daily life [Cicerone et al., 2011].

Traditional cognitive rehabilitation has demonstrated efficacy following ABI [Cicerone et al., 2019], yet several limitations constrain its applicability in severely disabled patients: reduced ecological validity, limited multisensory engagement, and poor tolerability in individuals with low arousal or motivation [Martínez-Moreno et al., 2016; Larson et al., 2014].

Virtual reality (VR) has emerged as a promising alternative, offering interactive, adjustable environments that foster active participation and deliver immediate multimodal feedback [Rizzo et al., 2004; Weiss et al., 2006]. Systematic reviews support VR efficacy in improving attention, executive functions, and visuospatial abilities after stroke and TBI, with outcomes comparable or superior to conventional therapy [Demeco et al., 2023; Riva et al., 2020; Wankhede et al., 2025].

ISSN: 3035-062X
2026, 3 (1)

Preliminary Reports and Negative Results in Life Science and Humanities

However, a critical and underexplored clinical gap remains: the application of VR in patients with severe ABI who are in the acute-to-subacute phase and require bedside delivery. Immersive head-mounted displays carry risk of cybersickness and are poorly tolerated in this population; non-immersive VR systems delivered via screen or tablet may offer greater safety, flexibility, and feasibility without requiring patients to be mobilized [Wu et al., 2020; Huygelier et al., 2021]. Despite these advantages, bedside non-immersive VR protocols specifically designed for severe ABI remain scarcely investigated.

The VESPA 2.0 software [Merlo et al., 2022] represents a candidate tool to address this gap. Originally validated in mild cognitive impairment (MCI), it provides ecologically grounded tasks combining auditory and visual feedback to target global cognition, visuospatial skills, and executive functions, with excellent tolerability [Latella et al., 2024]. Its task structure aligns with the mechanisms through which VR has been shown to drive neuroplastic recovery in ABI. Recent evidence supports specific sensitivity of VR-based training to attention and processing speed [Ponsford et al., 2024; Archives of Physical Medicine and Rehabilitation, 2025], orientation [Pastore et al., 2024], and visuospatial processing [Röhrig et al., 2020] in ABI populations, providing a coherent neuropsychological rationale for adapting VESPA 2.0 to this context.

Given the scarcity of evidence on bedside non-immersive VR in severe ABI, this study aims to evaluate the feasibility, safety, and preliminary efficacy of VESPA 2.0 adapted for cognitive rehabilitation in individuals with severe ABI. We hypothesized that VR tasks could be safely integrated into bedside rehabilitation and would yield improvements in attention, semantic memory, orientation, and processing speed.

Materials and Methods

Study design

An exploratory longitudinal pilot study was conducted. Given the small and heterogeneous nature of the sample, individual trajectories were analyzed using Kendall's Tau-U statistic, a nonparametric effect size suited for repeated-measures single-case data [Lee & Cherney, 2018]. While this approach shares methodological elements with single-case experimental designs, the present study did not incorporate multiple-baseline, reversal, or staggered introduction phases; therefore, causal inferences regarding treatment efficacy cannot be drawn.

ISSN: 3035-062X
2026, 3 (1)

Preliminary Reports and Negative Results in Life Science and Humanities

Participants

Six patients (4 males, 2 females; aged 23–59) with severe ABI due to traumatic brain injury (TBI, n=1), ischemic stroke (IS, n=4), or cerebral hemorrhage (CH, n=1) were enrolled at a neurorehabilitation unit. Sociodemographic and clinical characteristics of patients enrolled are shown in Table 1.

PATIENT	AGE/SEX	EDUCATION	MD	TIME FROM ABI ONSET	HS DURATION	STROKE PHASE	LESIONAL SITE
TBI_{P1}	35/M	8	R	11 months	104 days	C	Diffuse axonal injury
IS_{P1}	51/F	13	R	4 months	27 days	S	R-MCA territory
IS_{P2}	53/F	5	R	8 months	112 days	C	R-PL/OL
IS_{P3}	23/M	15	L	2 months	49 days	S	L-MCA territory
IS_{P4}	24/M	13	R	6 months	144 days	C	L- TL/PL, pwm
CH_{P1}	59/M	18	R	4 months	76 days	S	R- FL and bilateral FL-basal

Table 1. *Sociodemographic and clinical characteristics of the enrolled patients. Temporal and lesional descriptions were reported from patients' medical records. Legend: Male (M), Female (F), Manual dominance (Md), Hospital stay (Hs), right (R), left (L), Chronic (C), Subacute (S), Frontal lobe (FL), Parietal lobe (PL), Temporal lobe (TL), Occipital Lobe (OL), Periventricular White Matter (pwm).*

Inclusion and Exclusion Criteria

Participants were eligible for inclusion if they had a diagnosis of severe ABI, whether of traumatic, ischemic, or hemorrhagic origin. Additional inclusion criteria were the ability to engage with tablet-based tasks with null or minimal external support, as well as sufficient to tolerate cognitive intervention sessions lasting 30 to 45 minutes.

Patients were excluded if they presented with severe visual, motor, or language impairments that would preclude the execution of the experimental tasks. Further exclusion criteria included the presence of a progressive neurodegenerative disorder or a medical condition that might compromise participation in the study.

Standardized clinical assessment

All of the patients underwent a standardized clinical assessment at the beginning (t0), at the middle (t1) and at the end (t2) of the intervention. The assessment included the following scales:

- *Mini-Mental State Examination (MMSE)*: a brief standardized screening instrument for global cognitive functioning, assessing orientation, registration, attention, recall, language, and visuo-

ISSN: 3035-062X
2026, 3 (1)

Preliminary Reports and Negative Results in Life Science and Humanities

constructive abilities across 30 items. Total scores range from 0 (maximum cognitive impairment) to 30 (no impairment), with scores below 24 conventionally indicating cognitive dysfunction.

- *Rehabilitation Complexity Scale - Extended (RCS-E)*: measures the complexity of rehabilitation needs across medical, nursing, physiotherapy, and multidisciplinary care domains. Scores range from 0 to 25 or above depending on the version, with higher scores indicating greater rehabilitation complexity; accordingly, a decrease over time reflects clinical progress and reduced care burden.
- *Functional Independence Measure (FIM)*: a widely used measure of functional independence in activities of daily living, covering 18 items across motor (13 items) and cognitive (5 items) subscales. Each item is rated on a 7-point scale (1 = total assistance, 7 = complete independence), yielding a total score ranging from 18 (total dependence) to 126 (full independence). Higher scores indicate greater functional autonomy.
- *Barthel Index (BI)*: evaluates independence in ten basic activities of daily living, including feeding, bathing, dressing, and mobility. Total scores range from 0 (complete dependence) to 100 (full independence), with higher scores reflecting greater autonomy. It is among the most widely validated functional outcome measures in neurorehabilitation.

Intervention

VESPA 2.0 is a VR-based rehabilitation software originally developed for immersive cognitive training in individuals with MCI [Merlo et al. 2022]. For the present study, the system was adapted to a tablet interface to enable bedside use. Patients enrolled underwent a 12-week individualized cognitive VR training program structured in progressive modules with therapists providing supervision, verbal cues, and standardized feedback throughout the sessions. Each session lasted 30–45 minutes, was scheduled in late morning, when patients were most alert and was delivered 3 times weekly. Several modules were simplified or modified to accommodate the clinical needs and cognitive limitations of severe ABI population. The training tasks are described in table 2 and displayed in figure 1. Finally, at the end of the training program, each patient was asked to indicate whether they preferred traditional paper-and-pencil exercises or the non-immersive VR training system.

ISSN: 3035-062X
2026, 3 (1)

Preliminary Reports and Negative Results in Life Science and Humanities

***Table 2**: Overview of cognitive domains, tasks, and outcome measures assessed by the computerized battery. For each domain, the corresponding task, a brief description of the procedure, the outcome measure(s) used, and the range or unit of measurement are reported.* ***Legend**: Reaction Time (RT); Visual Sequence Reconstruction (SERE); Semantic Matching - Objects (SMo); Semantic Matching - Animals (SMa); Semantic Affinity Judgment (SAJ); Feature-Based Identification (F-BI); Semantic-Spatial Identification (SSI); accuracy (acc); milliseconds (ms); seconds (s); number of correct responses (n).*

DOMAIN	TASK	DESCRIPTION	OUTCOME MEASURES	RANGE/ UNITS
ORIENTATION TASK	Temporal Orientation	Date, weekday, month, year, season (5 items)	Cumulative score	0–5
	Spatial Orientation	Place, city, region, country, floor (5 items)	Cumulative score	0–5
	Autobiographical Knowledge	Name, birth date, occupation, family (4 items)	Cumulative score	0–4
REACTION TIME (RT)		Touch a red cube upon appearance; 15 trials, varying positions	Mean RT, Tot RT	ms / s
VISUAL SEQUENCE RECONSTRUCTION (SERE)		Reproduce a 10-item sequence (digits, letters, shapes, colors)	SeRe t	s
SEMANTIC MATCHING	Objects (SMo)	Name and match halves of fragmented object images	SMo t	s
	Animals (SMa)	Same as SMo with animal stimuli	SMa t, SMa acc	s / n
COGNITIVE DECISION TASK	Semantic Affinity Judgment (SAJ)	Judge semantic relatedness of 6 stimulus pairs	SAJ acc	n
	Feature-Based Identification (F-BI)	Select 1/3 stimuli based on a given feature: 6 triads	F-BI acc	n
	Semantic-Spatial Identification (SSI)	Identify spatial position of stimuli by feature; 4 presentations	SSI acc	n

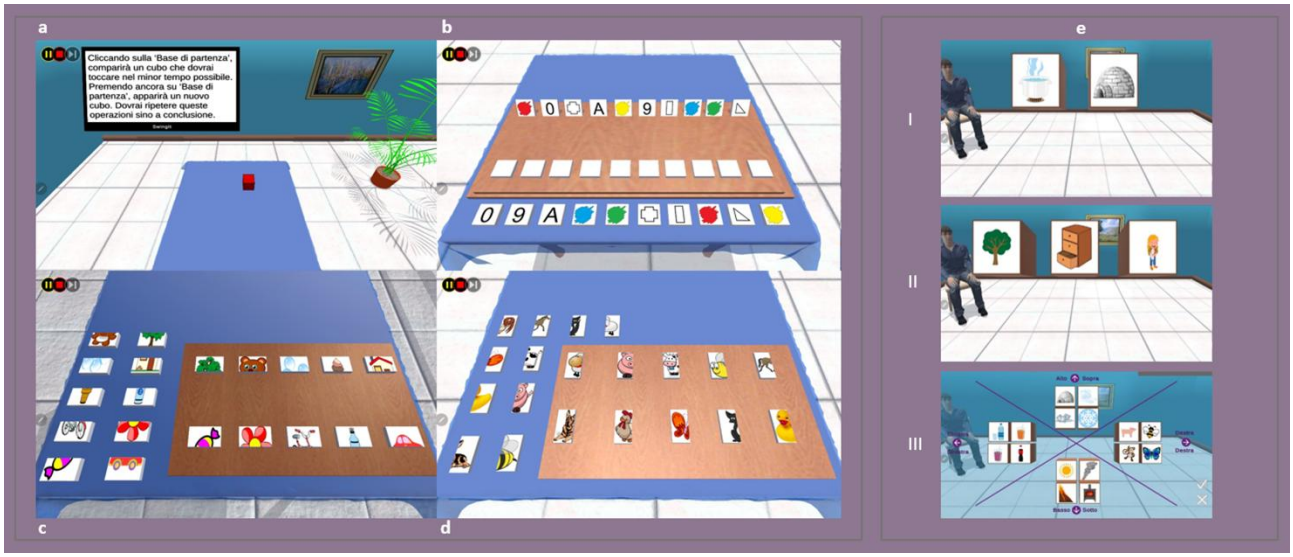

***Figure 1**: Virtual-reality tasks administered to patients. (a) RT task: locate and touch the red cube on the table as quickly as possible; (b) SeRe: reproduce a sequence of 10 figures by ordering the same drawings shown in random order; (c) SMo: recognize the fragmented object, name it, and match the two halves that belong together; (d) SMa: same as (c); but with animals. (e-I) SAJ: decide whether the pair of pictures is semantically related (yes/no); (e-II) F-BI: choose, among three images, the one that meets the instructed feature (e.g., taller; open/closed); (e-III) SSI: indicate the position (up/down/right/left) of the group of stimuli that matches the requested feature. For all tasks, response time and/or accuracy were recorded.*

ISSN: 3035-062X
2026, 3 (1)

Preliminary Reports and Negative Results in Life Science and Humanities

Statistical analysis

Clinical scales collected at baseline (t0), mid-treatment (end of the 6th week; t1), and post-treatment (t2) were analyzed at the group level. Overall longitudinal change was evaluated using the Friedman test, with Kendall's effect size. Significant effects were followed by Bonferroni-corrected Wilcoxon signed-rank post-hoc comparisons (adjusted $\alpha = .017$).

Individual VESPA task performance trajectories were subsequently analyzed using Tau-U, a nonparametric effect size based on Kendall's rank correlation, suited for repeated-measures single-case data [Lee & Cherney, 2018]. This statistic quantifies the nonoverlap between baseline (A) and intervention (B) phases while controlling for monotonic trends within phases. Values range from −1 to +1; for accuracy-based outcomes, positive values indicate improvement, whereas for time-based outcomes, negative values reflect faster performance. The contrast A vs. B + Trend B − Trend A was adopted as the primary index, as it removes pre-existing baseline trends potentially attributable to spontaneous neurological recovery while incorporating the directional trajectory observed during intervention, thus providing the most conservative estimate of treatment-related change. NA/NaN values indicate insufficient data or variability within a given phase.

Results

Six patients with severe acquired brain injury were enrolled (4 males, 2 females; mean age 40.8 ± 14.5 years, range 23–59). Etiology was traumatic brain injury in one patient, ischemic stroke in four, and cerebral hemorrhage in one. Participants had, on average, 12.0 ± 4.7 years of education (range 5–18). Manual dominance was predominantly right-handed (5/6), with one left-handed patient.

The mean time from ABI onset to study inclusion was 5.8 ± 3.3 months (range 2–11), with three patients assessed in the subacute phase and three in the chronic phase. The average hospital stay duration at the time of assessment was 85.3 ± 40.8 days (range 27–144).

Lesional sites, derived from neuroradiological reports and cross-checked with clinical documentation, predominantly involved middle cerebral artery territories and temporo-parietal or parieto-occipital regions (four ischemic strokes: two left, two right), with additional periventricular white matter involvement in one case. One patient presented with diffuse axonal injury after TBI, and one with right frontal and bilateral fronto-basal hemorrhagic lesions. Overall, lesions showed a slight predominance of right-hemisphere involvement (3/6), alongside two left-hemisphere and one diffuse lesion.

ISSN: 3035-062X
2026, 3 (1)

Preliminary Reports and Negative Results in Life Science and Humanities

Regarding to the four clinical scales administered at three time-points (t0, t1, t2) the Friedman test revealed a statistically significant overall change across time points for MMSE (\(\chi^2(2) = 11.273, p = .004, W = 0.939\)), FIM (\(\chi^2(2) = 10.333, p = .006, W = 0.861\)), and Barthel Index (\(\chi^2(2) = 10.000, p = .007, W = 0.833\)), all with large effect sizes indicating a highly consistent pattern of improvement across patients. The RCS-E approached but did not reach statistical significance (\(\chi^2(2) = 4.957, p = .084, W = 0.413\)), showing a moderate and directionally coherent reduction in rehabilitation complexity over time.
Scale trajectories across timepoints are reported in figure 2.

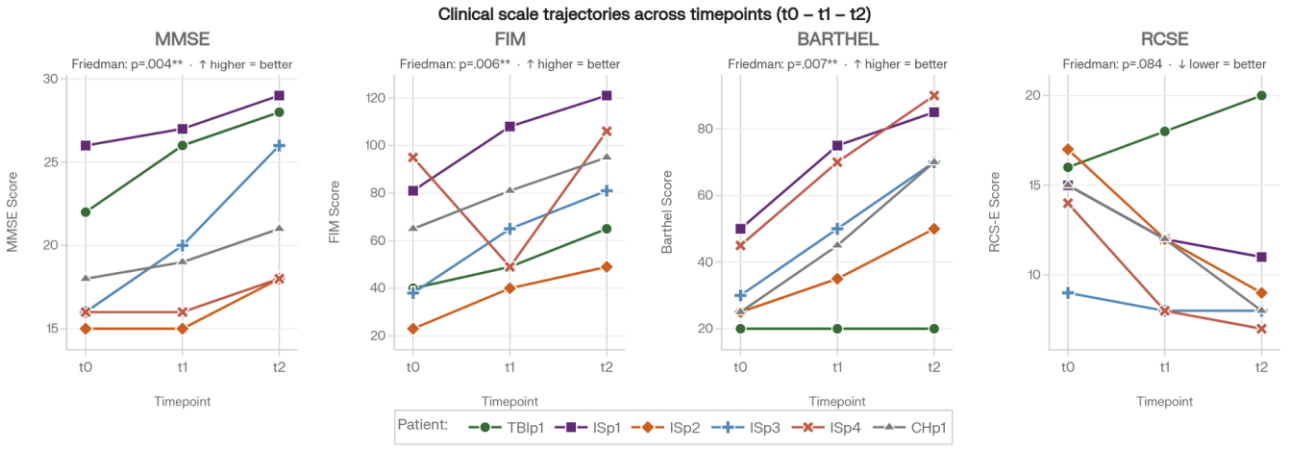

Figure 2: *Clinical scale trajectories across assessment time points (t0, t1, and t2) in the six enrolled patients. The figure shows individual longitudinal changes in MMSE, FIM, Barthel Index, and RCS-E scores during the 12-week VESPA 2.0 intervention. Overall, the plots indicate improvement in cognitive and functional outcomes over time, alongside a reduction in rehabilitation complexity.*

Bonferroni-corrected post-hoc Wilcoxon comparisons did not reach the adjusted significance threshold (*α* = .017) for any pairwise contrast, as expected given the limited statistical power associated with a sample of six participants. Nevertheless, trend-level effects were observed for MMSE (t1 vs. t2 and t0 vs. t2: \(p_{Bonf} = .094, r = 0.899\)) and FIM (t1 vs. t2 and t0 vs. t2: \(p_{Bonf} = .094, r = 0.899\)), with large effect sizes in both cases. For MMSE, median scores increased from 17.0 (IQR: 16.0–21.0) at t0, to 19.5 (IQR: 16.8–24.5) at t1, to 23.5 (IQR: 18.8–27.5) at t2. FIM median scores showed a similar trajectory, rising from 52.5 (IQR: 38.5–77.0) at t0 to 88.0 (IQR: 69.0–103.2) at t2. Barthel Index medians increased from 27.5 (IQR: 25.0–41.2) at t0 to 70.0 (IQR: 55.0–81.2) at t2, though post-hoc contrasts did not reach trend-level significance after correction (\(p_{Bonf} = .124–.127\)). RCS-E median scores decreased from 15.0 (IQR: 14.2–15.8) at t0 to 8.5 (IQR: 8.0–10.5) at t2, reflecting reduced care complexity, although no pairwise comparison reached even trend-level significance after Bonferroni correction.

ISSN: 3035-062X
2026, 3 (1)

Preliminary Reports and Negative Results in Life Science and Humanities

Overall, these findings indicate a consistent and clinically meaningful improvement in global cognitive functioning, functional independence, and rehabilitation complexity over the course of the protocol. Given the exploratory nature of these analyses and the small sample size, results should be regarded as hypothesis-generating and interpreted alongside the single-case Tau-U findings.

A summary of the VR-training results is provided in Table 1.

TBI$_{P1}$

Task· outcome¤	A·vs.·B¤	p· value¤	A·vs.·B¶ —·Trend·A¤	p· value¤	A·vs.·B¶ +·Trend· B¤	p· value¤	A·vs.·B·+·¶ Trend·B—· A¤	p· value¤
Mean·Rt¤	-1.00¤	.14¤	-0.95¤	.14¤	-0.95¤	.09¤	-0.95¤	.09¤
Tot·Rt¤	-1.00¤	.14¤	-0.58¤	.14¤	-0.33¤	.35¤	-0.33¤	.35¤
SMa·t¤	-1.00¤	.14¤	-0.60¤	.14¤	**-0.97¤**	**<.05*¤**	**-0.97¤**	**<.05*¤**
SMa·acc¤	0¤	NA¤	NaN¤	NA¤	NaN¤	NA¤	NaN¤	NA¤
SMo·t¤	-1.00¤	.14¤	-0.60¤	.14¤	**-0.97¤**	**<.05*¤**	**-0.97¤**	**<.05*¤**
SeRe·t¤	1.00¤	.13¤	0.62¤	.13¤	-0.21¤	.56¤	-0.21¤	.56¤
SAJ·acc¤	-0.89¤	.16¤	-0.63¤	.16¤	-0.73¤	.06¤	-0.73¤	.06¤
F-BI·acc¤	-0.89¤	.21¤	-0.54¤	.21¤	-0.70¤	.06¤	-0.70¤	.06¤
SSI·acc¤	-0.89¤	.16¤	-0.63¤	.16¤	-0.73¤	.06¤	-0.73¤	.06¤

IS$_{P1}$

Task· outcome¤	A·vs.·B¤	p· value¤	A·vs.·B¶ —·Trend·A¤	p· value¤	A·vs.·B¶ +·Trend· B¤	p· value¤	A·vs.·B·+·¶ Trend·B—·A¤	p· value¤
Mean·Rt¤	-1.00¤	.14¤	-0.58¤	.14¤	-0.60¤	.09¤	-0.60¤	.09¤
Tot·Rt¤	-1.00¤	.14¤	-0.58¤	.14¤	-0.60¤	.09¤	-0.60¤	.09¤
SMa·t¤	-0.60¤	.38¤	-0.35¤	.38¤	-0.47¤	.19¤	-0.47¤	.19¤
SMa·acc¤	-0.33¤	.65¤	-0.20¤	.65¤	0.35¤	.38¤	0.35¤	.38¤
SMo·t¤	-1.00¤	.14¤	-0.58¤	.14¤	-0.20¤	.56¤	-0.20¤	.56¤
SeRe·t¤	0.60¤	.38¤	0.35¤	.38¤	-0.20¤	.56¤	-0.20¤	.56¤
SAJ·acc¤	0.25¤	.75¤	0.13¤	.75¤	0.54¤	.15¤	0.54¤	.15¤
F-BI·acc¤	0¤	NA¤	NaN¤	NA¤	NaN¤	NA¤	NaN¤	NA¤
SSI·acc¤	0.33¤	.65¤	0.20¤	.65¤	-0.12¤	.77¤	-0.12¤	.77¤

IS$_{P2}$

Task· outcome¤	A·vs.·B¤	p· value¤	A·vs.·B¶ —·Trend·A¤	p· value¤	A·vs.·B¶ +·Trend· B¤	p· value¤	A·vs.·B·+·¶ Trend·B—·A¤	p· value¤
Mean·RT¤	-0.20¤	.77¤	-0.12¤	.77¤	0.33¤	.35¤	0.33¤	.35¤
Tot·RT¤	0.20¤	.77¤	0.12¤	.77¤	0.47¤	.19¤	0.47¤	.19¤
SMa·t¤	-0.89¤	.23¤	-0.48¤	.23¤	-0.55¤	.13¤	-0.55¤	.13¤
SMa·acc¤	**1.00¤**	**<.05*¤**	**1.00¤**	**<.05*¤**	0.58¤	.14¤	0.58¤	.14¤
SMo·t¤	-1.00¤	.14¤	-0.58¤	.14¤	-0.33¤	.35¤	-0.33¤	.35¤
SeRe·t¤	-0.89¤	.23¤	-0.48¤	.23¤	-0.28¤	.44¤	-0.28¤	.44¤
SAJ·acc¤	-0.89¤	.21¤	-0.54¤	.21¤	0.08¤	.84¤	0.08¤	.84¤
F-BI·acc¤	-0.75¤	.34¤	-0.40¤	.34¤	0.23¤	.54¤	0.23¤	.54¤
SSI·acc¤	0.89¤	.21¤	0.54¤	.21¤	0.23¤	.54¤	0.23¤	.54¤

IS$_{P3}$

Task· outcome¤	A·vs.·B¤	p· value¤	A·vs.·B¶ —·Trend·A¤	p· value¤	A·vs.·B¶ +·Trend· B¤	p· value¤	A·vs.·B·+·¶ Trend·B—·A¤	p· value¤
Mean·Rt¤	-1.00¤	.14¤	-0.58¤	.14¤	-0.20¤	.56¤	-0.20¤	.56¤
Tot·Rt¤	-1.00¤	.14¤	-0.58¤	.14¤	-0.20¤	.56¤	-0.20¤	.56¤
SMa·t¤	-0.60¤	.38¤	-0.35¤	.38¤	-0.47¤	.19¤	-0.47¤	.19¤
SMa·acc¤	0¤	NA¤	NaN¤	NA¤	NaN¤	NA¤	NaN¤	NA¤
SMo·t¤	0.44¤	.55¤	0.24¤	.55¤	0.14¤	.70¤	0.14¤	.70¤
SeRe·t¤	0.44¤	.55¤	0.24¤	.55¤	-0.41¤	.25¤	-0.41¤	.25¤
SAJ·acc¤	-0.44¤	.55¤	-0.24¤	.55¤	-0.28¤	.44¤	-0.28¤	.44¤
F-BI·acc¤	0.60¤	.35¤	0.39¤	.35¤	0.30¤	.42¤	0.30¤	.42¤
SSI·acc¤	-0.57¤	.48¤	-0.32¤	.48¤	-0.37¤	.35¤	-0.37¤	.35¤

IS$_{P4}$

Task· outcome¤	A·vs.·B¤	p· value¤	A·vs.·B¶ —·Trend·A¤	p· value¤	A·vs.·B¶ +·Trend· B¤	p· value¤	A·vs.·B·+·¶ Trend·B—·A¤	p· value¤
Mean·Rt¤	-0.60¤	.38¤	-0.35¤	.38¤	-0.60¤	.09¤	-0.60¤	.09¤
Tot·Rt¤	-0.60¤	.38¤	-0.35¤	.38¤	-0.60¤	.09¤	-0.60¤	.09¤
SMa·t¤	-0.20¤	-77¤	-0.12¤	.77¤	-0.41¤	.25¤	-0.41¤	.25¤
SMa·acc¤	0.60¤	.30¤	0.45¤	.30¤	0.60¤	.11¤	0.60¤	.11¤
SMo·t¤	-0.20¤	.77¤	-0.12¤	.77¤	-0.33¤	.35¤	-0.33¤	.35¤
SeRe·t¤	-1.00¤	.14¤	-0.58¤	.14¤	-0.20¤	.56¤	-0.20¤	.56¤
SAJ·acc¤	0.60¤	.30¤	0.45¤	.30¤	0.43¤	.26¤	0.43¤	.26¤
F-BI·acc¤	0.89¤	.22¤	0.52¤	.22¤	0.00¤	1.00¤	0.00¤	1.00¤
SSI·acc¤	1.00¤	.08¤	0.75¤	.08¤	0.09¤	.82¤	0.09¤	.82¤

CH$_{P1}$

Task· outcome¤	A·vs.·B¤	p· value¤	A·vs.·B¶ —·Trend·A¤	p· value¤	A·vs.·B¶ +·Trend· B¤	p· value¤	A·vs.·B·+·¶ Trend·B—·A¤	p· value¤
Mean·Rt¤	0.60¤	.38¤	0.35¤	.38¤	0.33¤	.35¤	0.33¤	.35¤
Tot·Rt¤	0.60¤	.38¤	0.35¤	.38¤	0.33¤	.35¤	0.33¤	.35¤
SMa·t¤	-0.25¤	.76¤	-0.13¤	.76¤	0.30¤	.42¤	0.30¤	.42¤
SMa·acc¤	0.00¤	1.00¤	0.00¤	1.00¤	-0.21¤	.56¤	-0.21¤	.56¤
SMo·t¤	-1.00¤	.12¤	-0.65¤	.12¤	-0.15¤	.69¤	-0.15¤	.69¤
SeRe·t¤	-0.75¤	.35¤	-0.39¤	.35¤	-0.30¤	.42¤	-0.30¤	.42¤
SAJ·acc¤	-0.75¤	.35¤	-0.39¤	.35¤	-0.45¤	.23¤	-0.45¤	.23¤
F-BI·acc¤	-1.00¤	.12¤	-0.65¤	.12¤	-0.30¤	.42¤	-0.30¤	.42¤
SSI·acc¤	-0.89¤	.23¤	-0.50¤	.23¤	-0.36¤	.33¤	-0.36¤	.33¤

***Table 2**. Overview of single-case effects (Tau-U) by task and patient; values reflect the trend-adjusted contrast (A vs. B + Trend B − Trend A). Negative (time) = faster; positive (accuracy) = better.*

ISSN: 3035-062X
2026, 3(1)
Preliminary Reports and Negative Results in Life Science and Humanities

successfully completed the 12-week VR-based cognitive training program. Across all sessions, no episodes of agitation, cybersickness, or other adverse events were observed, suggesting that the intervention was safe and well tolerated even in individuals with severe ABI. Therapists consistently reported good cooperation, and patients demonstrated sustained engagement throughout the training period.

Generally, all patients displayed positive training trajectories, although these changes did not always reach statistical significance. Two patients exhibited statistically significant improvements: the individual with traumatic brain injury (TBIp1) showed a marked reduction in completion times during semantic matching tasks (SMa and SMo) with a large effect size (Tau-U = −0.97, $p < .05$), while an ischemic stroke patient (ISp2), demonstrated significant gains in semantic accuracy on the animal categorization task (SMa acc), achieving a maximal effect (Tau-U = +1.00, $p < .05$).

The remaining four patients (ISp1, ISp3-4, CHp1) showed faster reaction times across tasks, with Tau-U values ranging from approximately −0.60 to −0.95. Moreover, some of these effects approached significance, with p-values around .09. One patient (CHp1) exhibited small positive Tau-U values, indicating slightly slower performance. In semantic matching tasks requiring fast responses, multiple patients (e.g., ISp4, CHp1) showed reduced completion times, though effect sizes remained below significance. Performance on cognitive decision-making tasks (SAJ, FBI, SSI) was more variable, with no consistent accuracy gains across the sample. Notably, patient ISp4 showed an accuracy improvement on the SSI task when considering the simple A vs. B contrast (Tau-U = +1.00, $p = .08$), but this effect did not remain significant after adjustment for baseline trends (Figure 3).

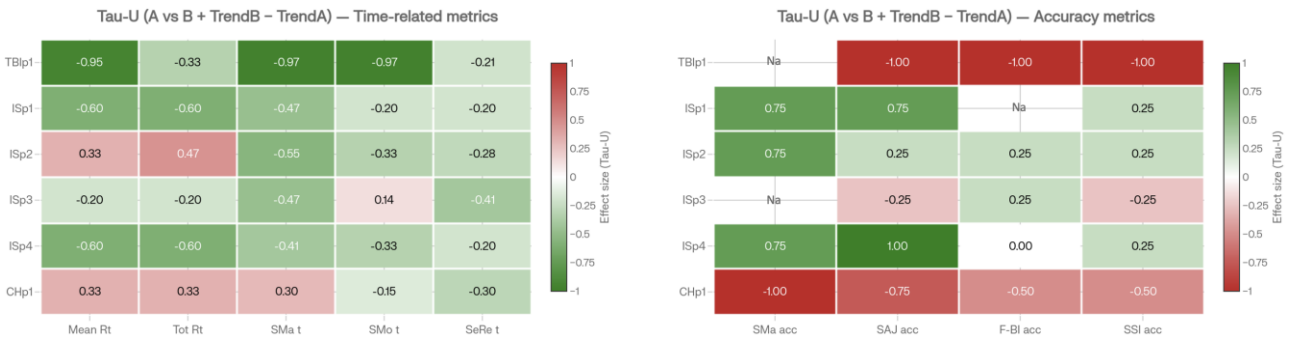

Figure 3. *Heatmaps of Tau-U effect sizes for the contrast A vs. B + Trend B − Trend A for Time-related (left) and Accuracy (right) measures. Rows represent individual patients (TBIp1 = traumatic brain injury; ISp1–ISp4 = ischemic stroke; CHp1 = cerebral hemorrhage), and columns represent task-specific outcomes. The color scale ranges from −1 to +1. For time-related measures (left panel), green indicates improvement (faster performance) and red indicates worsening (slower performance); for accuracy measures (right panel), green reflects improvement (higher accuracy) and red reflects deterioration (lower accuracy). Values near 0 indicate no meaningful change. Na = not applicable (task not computable for that patient in the given phase). Legend: Reaction Time (RT), Visual Sequence Reconstruction (SeRe), Objects (SMo), Animals (SMa), Semantic Affinity Judgment (SAJ), Feature-Based, Identification (F-BI), Semantic-Spatial Identification (SSI).*

ISSN: 3035-062X
2026, 3(1)
Preliminary Reports and Negative Results in Life Science and Humanities

Finally, regarding training preference, all six patients indicated a preference for the VR system, suggesting high acceptability of the software.

4. Discussion

The rehabilitation of patients with severe ABI, particularly those emerging from EMCS, remains a major clinical challenge. Recovery of higher-order cognitive functions following severe brain injury is typically slow and heterogeneous, and fluctuations in arousal and awareness can substantially limit participation in structured cognitive therapy [Giacino et al., 2014]. As a result, traditional cognitive rehabilitation approaches are difficult to implement consistently at the bedside, and the therapeutic window for early cognitive engagement is frequently underutilized.

New technologies such as VR offer a promising opportunity to deliver controlled, adaptable, and engaging stimulation even in patients with reduced responsiveness or limited mobility. Although the precise neurocognitive mechanisms underlying any observed effects remain speculative in the absence of direct evidence, several hypotheses can be advanced. The multimodal sensory stimulation inherent to VR environments, integrating synchronized visual and auditory feedback within ecologically valid task contexts, may promote attentional engagement through the recruitment of frontoparietal networks, while the goal-directed and performance-contingent structure of VR tasks could activate mesolimbic reward circuitry, thereby enhancing motivation and effortful cognitive processing [Georgiev et al., 2021; Tinga et al., 2016]. Repeated practice within near-realistic scenarios may further support experience-dependent neuroplasticity in perilesional tissue, potentially facilitating the gradual reactivation of semantic and attentional networks partially disrupted by the injury [Parsons, 2015]. These interpretations, however, remain entirely tentative and should be investigated in future studies incorporating neurophysiological measures such as EEG or fNIRS. Within this clinical context, this exploratory pilot study examined the feasibility, safety, and preliminary efficacy of VESPA 2.0, a non-immersive VR cognitive rehabilitation program for severe ABI.

Consistently with previous studies reporting minimal discomfort during VR-based training in neurologically vulnerable populations [Catania et al., 2023; Riva et al., 2020], all participants completed the 12-week protocol without agitation, cybersickness, or other adverse events, supporting the safety and tolerability of the intervention.

Among the six patients enrolled, trend-adjusted Tau-U analyses identified two statistically significant findings at the individual level. TBIp1 exhibited a large reduction in completion time on semantic matching tasks (SMa/SMo; Tau-U = −0.97, $p < .05$), and ISp2 demonstrated maximal accuracy on the

ISSN: 3035-062X
2026, 3(1)
Preliminary Reports and Negative Results in Life Science and Humanities

animal semantic matching task (SMa acc; Tau-U = +1.00, $p < .05$). These isolated findings are consistent with prior reports of VR-related improvements in processing speed and semantic functioning in ABI populations [Cardile et al., 2025; De Luca et al., 2023]; however, given the large number of comparisons performed across tasks, patients, and contrast types, the risk of type I error is elevated, and these results must be interpreted with considerable caution. No correction for multiple comparisons was applied across the full set of Tau-U analyses, which substantially limits the inferential weight of individual findings. The remaining four patients showed directionally favorable but non-significant Tau-U values across most tasks, which do not constitute evidence of treatment efficacy and should not be interpreted as meaningful trends. Performance on higher-order cognitive tasks (SAJ, F-BI, SSI) was heterogeneous across patients, with no consistent pattern of change across the sample. On the SSI task, ISp4 yielded a maximal unadjusted effect size (Tau-U = +1.00, $p = .08$) that was not confirmed after trend correction, illustrating the importance of accounting for spontaneous neurological recovery in post-acute ABI and the sensitivity of results to the choice of analytical contrast.

Secondary group-level analyses on four clinical scales showed significant overall Friedman effects for MMSE, FIM, and Barthel Index, with large Kendall's W values, and a non-significant result for RCS-E. These findings indicate that the group as a whole showed systematic changes in functional and cognitive measures over the course of the study; however, none of the Bonferroni-corrected pairwise comparisons reached statistical significance, and the small sample size (n = 6) precludes any firm conclusions regarding the contribution of the VR intervention relative to spontaneous recovery or other concurrent rehabilitation inputs. The absence of a control condition represents a critical limitation in this respect.

All patients reported preferring VR over traditional paper-and-pencil exercises, suggesting good acceptability and feasibility for bedside delivery. In addition to offering enhanced ecological validity and adaptable task difficulty [Brundage et al., 2006; Tieri et al., 2018], the VR format may support patient engagement and compliance, factors that, while clinically relevant, cannot substitute for controlled efficacy evidence.

The present study has several important limitations that constrain the interpretation of its findings. The sample was small (n = 6) and etiologically heterogeneous, encompassing traumatic brain injury, ischemic stroke, and cerebral hemorrhage across widely varying lesion sites, stroke phases, and functional levels. The absence of a control condition precludes causal attribution of any observed changes to the intervention. The large number of outcome measures, spanning multiple tasks, contrasts, and time points, substantially inflates the risk of false-positive findings, and no global correction for multiplicity was applied. The study also lacks extended follow-up, limiting any inference regarding the durability of observed changes. These factors collectively restrict the generalizability of findings and preclude any

ISSN: 3035-062X
2026, 3(1)
Preliminary Reports and Negative Results in Life Science and Humanities

recommendation for clinical implementation at this stage. Future studies should incorporate an active control condition, pre-register primary outcomes, apply appropriate correction for multiple comparisons, stratify analyses by etiology and lesion site, and include longer follow-up assessments. Mechanistic investigations incorporating neurophysiological measures such as EEG, fNIRS, or eye-tracking would help clarify the neural correlates of any training-related change, while multicenter designs with larger samples are necessary to generate interpretable effect size estimates.

In conclusion, VESPA 2.0 was feasible, safe, and well tolerated in a pilot sample of patients with severe ABI. Two statistically significant individual-level effects were identified, but these findings must be contextualized within the limitations of an uncontrolled exploratory design with multiple outcomes and no correction for multiplicity. The present results are best regarded as preliminary and hypothesis-generating, providing a rationale for adequately powered, controlled trials such as that proposed by Magliacano et al. [2025].

Ethical approval: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of IRCCS Centro Neurolesi Bonino-Pulejo (No. 27/2025-03/11/2025).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest statement: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding: This work was supported by Current Research Funds 2026, Ministry of Health, Italy.

Acknowledgments: None

Author Contributions: Conceptualization: C.D., T.F.; Data curation: M.M.G., L.D., C.L.; Formal analysis: M.D.; Investigation: D.H., C.R., M.A. D.L.R.; Methodology: C.F., R.C.; Resources: P.S.M., G.N., C.L.; Supervision: T.F., Q.A., C.R.S.; Validation: H.D., A.M., C.R., D.L.R.; Visualization: G.N., M.D.; Writing – original draft: C.D., T.F.; Writing – review & editing: C.D., T.F., C.R.S.

ISSN: 3035-062X
2026, 3(1)
Preliminary Reports and Negative Results in Life Science and Humanities

References

Brassel, S., Power, E., Campbell, A., Brunner, M., & Togher, L. (2021). Recommendations for the design and implementation of virtual reality for acquired brain injury rehabilitation: Systematic review. Journal of Medical Internet Research, 23(7), e26344. https://doi.org/10.2196/26344.

Brundage, S. B., Graap, K., Gibbons, K. F., Ferrer, M., & Brooks, J. (2006). Frequency of stuttering during challenging and supportive virtual reality job interviews. Journal of fluency disorders, 31(4), 325–339. https://doi.org/10.1016/j.jfludis.2006.08.003.

Cardile, D., Arena, C., Corallo, F., Giuffrida, G. M., Giustiniani, A., Maggio, M. G., Rifici, C., Quartarone, A., Tomaiuolo, F., & Calabrò, R. S. (2025). A systematic review on the use of virtual reality in post-stroke patients: Exploring when modalities make the difference in executive and motor recovery. Frontiers in Virtual Reality, 6, Article 1653968. https://doi.org/10.3389/frvir.2025.1653968.

Catania, V., Rundo, F., Panerai, S., & Ferri, R. (2023). Virtual Reality for the Rehabilitation of Acquired Cognitive Disorders: A Narrative Review. Bioengineering (Basel, Switzerland), 11(1), 35. https://doi.org/10.3390/bioengineering11010035.

Cicerone, K. D., Langenbahn, D. M., Braden, C., Malec, J. F., Kalmar, K., Fraas, M., Felicetti, T., Laatsch, L., Harley, J. P., Bergquist, T., Azulay, J., Cantor, J., & Ashman, T. (2011). Evidence-based cognitive rehabilitation: Updated review of the literature from 2003 through 2008. Archives of Physical Medicine and Rehabilitation, 92(4), 519–530. https://doi.org/10.1016/j.apmr.2010.11.015.

Cicerone, K. D., Goldin, Y., Ganci, K., Rosenbaum, A., Wethe, J. V., Langenbahn, D. M., Malec, J. F., Bergquist, T. F., Kingsley, K., Nagele, D., Trexler, L., Fraas, M., Bogdanova, Y., & Harley, J. P. (2019). Evidence-Based Cognitive Rehabilitation: Systematic Review of the Literature From 2009 Through 2014. Archives of physical medicine and rehabilitation, 100(8), 1515–1533. https://doi.org/10.1016/j.apmr.2019.02.011.

Demeco, A., Zola, L., Frizziero, A., Martini, C., Palumbo, A., Foresti, R., & Barletta, M. (2023). Immersive virtual reality in post-stroke rehabilitation: A systematic review. Sensors, 23(3), 1712. https://doi.org/10.3390/s23031712.

ISSN: 3035-062X
2026, 3(1)
Preliminary Reports and Negative Results in Life Science and Humanities

De Luca, R., Bonanno, M., Marra, A., Rifici, C., Pollicino, P., Caminiti, A., Castorina, M. V., Santamato, A., Quartarone, A., & Calabrò, R. S. (2023). Can Virtual Reality Cognitive Rehabilitation Improve Executive Functioning and Coping Strategies in Traumatic Brain Injury? A Pilot Study. Brain sciences, 13(4), 578. https://doi.org/10.3390/brainsci13040578.

Figeys, M., Koubasi, F., Hwang, D., Hunder, A., Miguel-Cruz, A., & Ríos Rincón, A. (2023). Challenges and promises of mixed-reality interventions in acquired brain injury rehabilitation: A scoping review. International journal of medical informatics, 179, 105235. https://doi.org/10.1016/j.ijmedinf.2023.105235.

Giacino, J. T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D. I., Kelly, J. P., Rosenberg, J. H., Whyte, J., Zafonte, R. D., & Zasler, N. D. (2004). The minimally conscious state: Definition and diagnostic criteria. Neurology, 58(3), 349–353. https://doi.org/10.1212/WNL.58.3.349

Giacino, J., Fins, J., Laureys, S. et al. Disorders of consciousness after acquired brain injury: the state of the science. Nat Rev Neurol 10, 99–114 (2014). https://doi.org/10.1038/nrneurol.2013.279.

Huygelier, H., Mattheus, E., Abeele, V. V., Van Ee, R., & Gillebert, C. R. (2021). The use of the term virtual reality in post-stroke rehabilitation: A scoping review and commentary. Psychologica Belgica, 61(1), 145–162. https://doi.org/10.5334/pb.1069

Larson, E. B., Feigon, M., Gagliardo, P., & Dvorkin, A. Y. (2014). Virtual reality and cognitive rehabilitation: a review of current outcome research. NeuroRehabilitation, 34(4), 759–772. https://doi.org/10.3233/NRE-141078.

Latella, D., Formica, C., Ielo, A., Grioli, P., Marra, A., Costanzo, D., Merlo, M. E., Pappalardo, S. M., Corallo, F., Marino, S., Quartarone, A., Calabrò, R. S., & Maresca, G. (2024). A feasibility and usability study of a virtual reality tool (VESPA 2.0) for cognitive rehabilitation in patients with mild cognitive impairment: an ecological approach. Frontiers in psychology, 15, 1402894. https://doi.org/10.3389/fpsyg.2024.1402894.

Lee, J. B., & Cherney, L. R. (2018). Tau-U: A quantitative approach for analysis of single-case experimental data in aphasia. American Journal of Speech-Language Pathology, 27(1S), 495–503. https://doi.org/10.1044/2017_AJSLP-16-0197.

Magliacano, A., Fiorentino, M. R., Scarano, G., Colella, M., Fasano, C., Spinola, M., Monda, A., Estraneo, A., & VR-sABI study group (2025). Non-immersive virtual reality for cognitive rehabilitation of individuals with

ISSN: 3035-062X
2026, 3(1)
Preliminary Reports and Negative Results in Life Science and Humanities

severe acquired brain injury (VR-sABI): study protocol for a multicentric randomized controlled trial. Trials, 26(1), 392. https://doi.org/10.1186/s13063-025-09128-7.

Martínez-Moreno, J. M., Sánchez-González, P., Luna, M., Roig, T., Tormos, J. M., & Gómez, E. J. (2016). Modelling Ecological Cognitive Rehabilitation Therapies for Building Virtual Environments in Brain Injury. Methods of information in medicine, 55(1), 50–59. https://doi.org/10.3414/ME15-01-0050.

Merlo, E. M., Myles, L. A. M., & Pappalardo, S. M. (2022). The VESPA Project: Virtual Reality Interventions for Neurocognitive and Developmental Disorders. Journal of Mind and Medical Sciences, 9(1), 16–27. https://doi.org/10.22543/7674.91.P1627.

Parsons, T. D. (2015). Virtual reality for enhanced ecological validity and experimental control in the clinical, affective and social neurosciences. Frontiers in Human Neuroscience, 9, 660. https://doi.org/10.3389/fnhum.2015.00660.

Riva, G., Mancuso, V., Cavedoni, S., & Stramba-Badiale, C. (2020). Virtual reality in neurorehabilitation: a review of its effects on multiple cognitive domains. Expert review of medical devices, 17(10), 1035–1061. https://doi.org/10.1080/17434440.2020.1825939.

Rizzo, A. A., Schultheis, M., Kerns, K. A., & Mateer, C. (2004). Analysis of assets for virtual reality applications in neuropsychology. Neuropsychological Rehabilitation, 14(1–2), 207–239. https://doi.org/10.1080/09602010343000183.

Rose, F. D., Brooks, B. M., & Rizzo, A. A. (2005). Virtual reality in brain damage rehabilitation: review. Cyberpsychology & behavior: the impact of the Internet, multimedia and virtual reality on behavior and society, 8(3), 241–271. https://doi.org/10.1089/cpb.2005.8.241

Tagliaferri, F., Compagnone, C., Korsic, M., Servadei, F., & Kraus, J. (2006). A systematic review of brain injury epidemiology in Europe. Acta Neurochirurgica, 148(3), 255–268. https://doi.org/10.1007/s00701-005-0651-y.

Tate, R. L., McDonald, S., Perdices, M., Togher, L., Schultz, R., & Savage, S. (2008). Rating the methodological quality of single-subject designs and n-of-1 trials: introducing the Single-Case Experimental Design (SCED) Scale. Neuropsychological rehabilitation, 18(4), 385–401. https://doi.org/10.1080/09602010802009201.

ISSN: 3035-062X
2026, 3(1)
Preliminary Reports and Negative Results in Life Science and Humanities

Tieri, G., Morone, G., Paolucci, S., & Iosa, M. (2018). Virtual reality in cognitive and motor rehabilitation: Facts, fiction and fallacies. Expert Review of Medical Devices, 15(2), 107–117. https://doi.org/10.1080/17434440.2018.1425613.

Voinescu, A., Sui, J., & Stanton Fraser, D. (2021). Virtual reality in neurorehabilitation: An umbrella review of meta-analyses. Journal of Clinical Medicine, 10(7), 1478. https://doi.org/10.3390/jcm10071478.

Wankhede, N. L., Koppula, S., Ballal, S., Doshi, H., Kumawat, R., Raju, S., Arora, I., Sammeta, S. S., Khalid, M., Zafar, A., Taksande, B. G., Upaganlawar, A. B., Gulati, M., Umekar, M. J., Kopalli, S. R., & Kale, M. B. (2025). Virtual reality modulating dynamics of neuroplasticity: Innovations in neuro-motor rehabilitation. Neuroscience, 566, 97–111. https://doi.org/10.1016/j.neuroscience.2024.12.040.

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

Wilson, B. A. (2008). Neuropsychological rehabilitation. Annual Review of Clinical Psychology, 4, 141–162. https://doi.org/10.1146/annurev.clinpsy.4.022007.141212.

World Health Organization. (2006). Neurological disorders: Public health challenges. WHO Press.

Wu, B., Yu, X., & Gu, X. (2020). Effectiveness of immersive virtual reality using head-mounted displays on learning performance: A meta-analysis. British Journal of Educational Technology, 51(6), 1991–2005. https://doi.org/10.1111/bjet.13023.