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RATIONALE FOR THE STUDY

Robotic therapy is a well-established approach for upper limb rehabilitation in neurological and neurodegenerative populations, allowing clinician teams to increase the intensity and standardization of therapy. A key strength of robotic therapy is the possibility to personalize treatment in real-time based on a patient's performance, offering therapy that tailors the levels of difficulties, intensity, required movements, assistance levels, and workspace according to the patient's progress. This feature not only enhances motor recovery but also improves engagement and motivation, promoting neuroplasticity—a critical factor in the long-term recovery of neurological functions. In a Cochrane Review on cognitive rehabilitation for attention deficits[1] , the authors highlight that improving attention, also in the short term, is very important during motor and functional rehabilitation programs because high attention may enable people to engage better with the exercises proposed with a high ability to cope with proposed tasks. Given the inter-relationship between cognitive and motor functions, improvements in motor skills may not always lead to functional gains in activities of daily living without addressing cognitive impairments. For instance, deficits in attention and executive functioning can hinder a patient's ability to perform daily tasks despite motor recovery. This highlights the necessity for a more integrated approach to rehabilitation that concurrently addresses both motor and cognitive domains. In the last years, robotics rehabilitation, has included exercises stimulating cognitive functions, which can be proposed and performed during motor exercises. Several studies confirmed the high prevalence of cognitive impairment in neurological and neurodegenerative disorders[2-7] underlining its significant influence on motor learning strategies[8], functional recovery, and quality of life. Nevertheless, usually, the aim of the robotic treatment is the

improvement in motor performance and activities of daily living, while the cognitive deficits are often ignored or treated separately from motor impairment. A cognitive treatment is crucial for the subjects in which cognitive and motor impairments are often present at the same time, such as neurological patients[9] . Many studies have found that improvements in upper limb motor function do not always lead to progress in activities of daily living, such as dressing or eating. This may be because cognitive impairments, which often accompany motor issues, are not sufficiently addressed. Few studies explored the cognitive effects of a robotic rehabilitation program[10-11], and they did not use tools to investigate specific cognitive functions. After upper limb robotic treatment, all the explored cognitive domains significantly improved, such as attention and processing speed, visuospatial abilities, visual memory, executive functions, and memory. The implementation of cognitive tasks within robotic therapy, such as dual-task or feedback mechanisms, has the potential to stimulate cognitive processes directly linked to everyday functioning, including memory, visuospatial abilities, and problem-solving.[12] This can promote neuroplasticity by simultaneously engaging multiple brain networks, thereby promoting broader neurological recovery. Moreover, robotic devices ensure consistent and reproducible therapy. Intensive and repetitive rehabilitation training are essential for regaining motor functions, which can be challenging to achieve with traditional therapy[13]. An adaptive robotic training offers unique advantages for neurological and neurodegenerative patients, as well as the capacity to adjust task difficulty in real-time to ensuring the patient remains cognitively engaged. This continuous engagement is essential to improve neuroplasticity mechanisms that support both motor and cognitive recovery. Robotic therapy is not only as effective but potentially more beneficial in specific cases due to its precision and customization[14]. Several studies, including systematic reviews, have shown that robot training not only improves activities of daily living but also enhances muscle strength and function in the affected arm[15]. Two recent large-scale studies further support this, demonstrating that robotic therapy is at least as effective as conventional therapy in improving motor outcomes[16]. The most recent meta-analysis suggests that robotics can improve upper limb motor function and muscle strength[15], and, when compared to a similar amount of conventional therapy, no significant differences in terms of motor recovery are detected[17]. In fact, some research suggests that robotic-

assisted rehabilitation might provide an edge due to its precision and ability to customize the difficulty of each task, offering a personalized and engaging approach[18]. The limited focus on cognitive rehabilitation in existing studies may contribute to better outcomes, as well as patients with concurrent cognitive deficits may not fully benefit from motor rehabilitation alone. A systematic review revealed that only 15% of stroke rehabilitation trials included patients with cognitive impairments, underscoring a significant research gap that needs to be addressed to improve the inclusivity and efficacy of robotic interventions. The efficacy of robotics in recovering cognitive deficits was few explored. To date, the implementation of new graphical interfaces and more ecological scenarios, as well as more cognitively demanding tasks, can allow an active physical and cognitive engagement of patients during robotic therapy, due to a variety of solutions with different levels of technology, assistance, and complexity of exercises. This can be promoted through adaptive assistance, cognitive challenge[19], visual and auditory feedback to enhance patient's engagement[20] facilitating neuronal reorganization in the motor cortex [21-22-23-24-25].

The present study aims to assess the effectiveness of upper limb rehabilitation using robotics and virtual reality, comparing it to conventional therapy. The objective is to demonstrate that this innovative approach leads to more significant improvements in both motor and cognitive outcomes. Both the experimental and control groups will follow a rehabilitation program that involves not only the upper limb but also other body regions. The comparison between the two groups will be based on the analysis of cognitive and motor outcomes achieved in relation to upper limb rehabilitation. Therefore, we hypothesize that a robotic treatment, based on the execution of selected exercises, based on concurrent motor/cognitive tasks can improve cognitive deficits beyond motor function in patients with neurological and neurodegenerative disorder. The current study evaluates the cognitive effects of upper limb robotic rehabilitation training in neurological and neurodegenerative conditions.

OBJECTIVES OF THE STUDY

Assess the efficacy of sensor-based robotic rehabilitation training on cognitive functioning in patients with neurological and neurodegenerative disorders versus conventional therapies.

Primary Objectives:

- Evaluate the effect of robotic rehabilitation on specific cognitive domains (e.g. attention, memory, executive functions, visual-spatial perception) in patients with neurological and neurodegenerative disorders.

  Criteria for the primary outcome:

  - Parkinson's Disease: The ACE-R (Addenbrooke's Cognitive Examination-Revised) will be used to measure improvement, where significant progress in at least 2 subscales will indicate effective cognitive rehabilitation.
  - Multiple sclerosis: The Rao's Brief Repeatable Battery will assess cognitive function, with improvement in at least 2 subscales indicating significant recovery.
  - Stroke: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) will be used, with a significant cognitive improvement marked by an increase of 10 points.

Secondary Objectives:

- Analyze the correlation between specific cognitive deficits and motor recovery in patients undergoing robotic rehabilitation training
- Investigate the role of motor rehabilitation integrated with cognitive tasks in improving cognitive and motor functions.
- Analyse the impact of robotic rehabilitation on mood and psychological well-being.
- Compare the effectiveness of robotic rehabilitation training among different subgroups of neurological patients (Stroke- Multiple sclerosis- Parkinson's disease).

- Explore the influence of individual patient characteristics (age, severity of cognitive impairment, disease stage) on cognitive rehabilitation outcomes.

STUDY DESIGN

This study is designed as a randomized controlled trial with parallel groups aimed at evaluating the effectiveness of upper limb rehabilitation using robotics and virtual reality in comparison to conventional therapy. The primary objective is to demonstrate that this innovative approach leads to more significant improvements in both motor and cognitive outcomes.

Both the experimental and control groups will follow a structured rehabilitation program that involves not only the upper limb but also other body regions, ensuring a comprehensive approach to functional recovery. The experimental group will undergo robotic and virtual reality-based training, while the control group will receive conventional therapy. The comparison between the two groups will be based on the analysis of cognitive and motor outcomes related to upper limb rehabilitation, allowing for an in-depth assessment of the potential advantages offered by robotic therapy.

STUDY POPULATION

This study will employ purposive sampling to select participants. Purposive sampling is a non-probability sampling technique used when specific criteria are required to ensure the sample aligns with the research objectives. Purposive sampling ensures that all participants had similar characteristics relevant to the study's aims. Subjects who meet all inclusion criteria will be enrolled in the study and will be divided into two groups:

- Sensor-Based Robotic Rehabilitation Group (SBRR)
- Standard Conventional Therapy Group (SCT)

Sample Size

A power analysis was conducted using G*Power to determine the appropriate sample size for detecting a low to moderate effect (d = 0.4) with a paired t-test, a two-tailed significance level of 0.05, and a desired power of 0.80. The analysis indicates that a minimum of 52 participants per group is necessary to achieve sufficient statistical power for detecting significant changes within each group. Accounting for a potential dropout rate of 20%, the adjusted sample size is 63 per 3 participants per group.

METHODS AND PROCEDURES OF THE STUDY

The current study will follow the following timeline:

T0. Baseline: Initially, patients will be recruited and randomly assigned to one of two groups using block randomization. This method divides participants into small blocks and assigns an equal number of patients to each group within each block. For example, in a block of four participants, two will be assigned to group A and two to group B. This process is repeated for each block, ensuring that both groups have a balanced number of participants throughout the study.

SBRR will receive motor and cognitive rehabilitation assisted by robotic and sensor-based devices through Motore, Armeo Senso, Hand Tutor, Armeo Power, Armeo Spring, Pablo, Amadeo, Diego.

SCT will receive conventional motor rehabilitation treatment.

Subsequently, patients will undergo a neurological examination, comprehensive neuropsychological assessment, and motor evaluation. These assessments will be conducted in a blinded modality, with evaluators distinct from recruiters and therapists. Importantly, the evaluators will not be aware of the group assignment of the patients.

Following these assessments, both groups will engage in their respective rehabilitation programs. Each session will perform for 60 minutes 2-3 times a week for a total of 25 sessions.

T1. Post-intervention assessment: At the end of the rehabilitation program, a comprehensive neuropsychological and motor assessment will be conducted again.

Cognitive Assessment:

Each participant will undergoing by a neuropsychological evaluation before (T0) and immediately after the end of the robotic training (T1). The evaluation will conducted by neuropsychologist to ensure that cognitive assessments and interpretations of results remain unbiased and objective. We considered to used different neuropsychological tests to indagate specific cognitive domains to obtain a more complete neuropsychologic profile.

Parkinson population

For this target, the assessment will included a global cognitive evaluation using: Addenbroke's Cognitive Examination Revised (ACE-R)[26] was designed as a valid screening instrument for cognitive profile. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuo-spatial skills, conceptual reasoning and orientation; Wisconsin Card Sorting Test (WCST)[27] assesses executive functioning, in particular, cognitive flexibility in problem solving, inability to abstraction and perseverance; Corsi Block-Tapping Test evaluates span of visual-spatial memory[28]; Trail Making Test (TMT)[29] assesses selective attention and cognitive flexibility; Rey-Osterrieth Complex Figure Test[30] assesses visual-constructive and visual-spatial memory capabilities; Symbol Digit Modalities Test (SDMT)[31] examines sustained attention and working memory; Parkinson's disease questionnaire-39 (PDQ-39)[32] is a 39-item self-report questionnaire, which assesses Parkinson's disease-specific health related quality in 8 dimensions: Activities of Daily Living,Attention, Working Memory, Cognition, Communication, Depression, Functional Mobility, Social Relationships and support.

Multiple Sclerosis population

For this target, the assessment will included a global cognitive evaluation using: Brief Repeatable Neuropsychological Test (BRNT)[33] that includes several sub-tests to assess memory, attention, and executive functions, specifically designed for multiple sclerosis; The MSQOL-54[34] is a multidimensional health-related quality of life measure that combines both generic and MS-specific items into a single instrument.

Stroke population

For this target, the assessment will included a global cognitive evaluation using: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[35] is a brief, individually administered test that helps determine the neuropsychological status. It includes different cognitive tasks: attention and concentration, executive functions, memory, language, visuo-spatial skills, conceptual reasoning

and orientation tasks; Tower of London (TOL)[36] assesses the ability to plan and solve complex problems; Rey-Osterrieth Complex Figure Test assesses visual-constructive and visual-spatial memory capabilities; Stroke Specific Quality of Life Scale (SSQOL)[37] assesses several domains, including physical function, cognition, emotions, communication, and social life.

At the end of the rehabilitative training we used a scale for evaluate the main dimensions of usability by using System Usability Scale robotic (SUS-r)[38] and Goal Attainment Scaling (GAS)[39].

Motor Assessment:

Each participant will undergoing by a motor evaluation before (T0) and immediately after the end of the robotic training (T1). The evaluation will conducted by physiotherapist. It includes: Fugl-Meyer Assessment – Upper Limb (FMA-UL)[40] comprises of five domains: motor functioning (in the upper and lower extremities), sensory functioning, balance, joint range of motion and joint pain. It includes items assessing movement, coordination, and reflex action of the shoulder, elbow, forearm, wrist, hand; Motricity Index (MI)[41] for the upper limb assess upper extremity function and functional mobility; Disability of the Arm, Shoulder and Hand (DASH)[42] assesses musculoskeletal disorders of the shoulder, hand and arm; Nine Hole Peg Test (9HPT)[43] and Box and Block Test (BBT)[44] measure unilateral gross manual dexterity; Test del monofilamento di Semmes Wilson assesses whether alterations in skin sensitivity are present.

Inclusion criteria

- Age 18-75 years;
- FMA-UL 0-31: eligible for exoskeletons and robotic devices with high support. (Armeo Power, Amadeo, Motore)
- FMA-UL 32-47: eligible for end-effectors with medium support. (Armeo Spring, Hand Tutor, Diego)
- FMA-UL 48-52: eligible for sensor-based with low support. (Pablo, Diego, Armeo Senso)
- MoCA: ≤ 20

Exclusion criteria

- Severe cognitive disorders
- Behavioral disorders
- Sensory disorders

DURATION OF THE STUDY

The study duration will be 60 months.

STATISTIC ANALYSIS

A descriptive analysis of the sample will be performed for socio-demographic and clinical variables. The Shapiro-Wilk test will be applied to assess the distribution type of the variables. Continuous variables will then be expressed as mean±SD, while categorical variables will be presented as frequencies and percentages. The parameters evaluated will include the motor and cognitive test scores.

- For intra-group analysis, a paired T-test or Wilcoxon signed-rank test will be applied, depending on the data type, to compare the scores between the two time points. Additionally, the Pearson correlation coefficient will be calculated for parametric data, or Spearman's correlation for non-parametric data, to examine whether a relationship exists between demographic and clinical variables. Multiple regression analyses will be performed on the cognitive scores treated as dependent variables. Initially, we will focus on the influence of motor scores as predictors. A backward elimination stepwise procedure will be applied to select the best predictive variables according to the Akaike Information Criterion (AIC).
- For inter-group analysis, an unpaired T-test or Mann-Whitney U test will be applied to compare the groups at T0 and T1. Additionally, ANCOVA will be used with T1 cognitive scores as the dependent variable, group (SBRR vs. SCT) as the independent variable, and T0 cognitive scores and age as covariates, to determine whether the rehabilitation method (SBRR vs. SCT) has a true effect on cognitive improvement independent of baseline scores and age.

All analyses will be conducted using the open-source software package R4.2.2. A 95% confidence level will be established, with an alpha error of 5%. Statistical significance will be set at $p < 0.05$.

ETHICAL ASPECTS

The principal investigator (PI) will conduct the study in accordance with the rules of good clinical practice (GCP) and current legislation and in accordance with the current version of the Declaration of Helsinki.

Informed consent

Written informed consent will be obtained from all study participants, in accordance with current regulations. The investigator will inform each patient that participation in the study is voluntary and that refusal will not result in the loss of any benefits or adversely affect their relationship with the doctor. Before enrolling in the study, each subject will receive a comprehensive explanation about the nature and purpose of the study from the investigator. They will also be provided with a clear information sheet detailing all important aspects, allowing them the opportunity to ask any questions. The subject will have the right to take the necessary time to consider before signing the informed consent (IC), of which they will receive a copy. One of the original copies of the IC will be retained by the investigator.

Innovative Contribution of the Research and Expected Outcomes

This study offers an integrated approach to rehabilitation by simultaneously addressing motor and cognitive impairments. Traditional therapies focus primarily on motor recovery, often overlooking cognitive deficits that critically influence functional independence and quality of life.[1,2] Research aims to enhance attention, executive functions, memory, and visuospatial abilities while promoting motivation and engagement through adaptive and personalized interventions. [17,21] This dual focus leverages neuroplasticity by activating multiple brain networks, potentially achieving more robust recovery outcomes.[12,22] Expected results include improved cognitive and motor functions, optimized rehabilitation protocols, enhanced patient engagement, and better quality of life. The findings aim to establish evidence-based guidelines for integrating cognitive tasks into robotic rehabilitation, advancing current clinical practices.[19,20]

Protection of subject data

Before conducting any examinations required by this protocol, patients will also provide all the authorizations mandated by law, including those required in the European Regulation 2016/679 and Legislative Decree 196/2003 as amended by Legislative Decree No. 101 of 10/08/2018. In adherence to the principles of good clinical practice, each subject will be assigned a unique code that will serve as their identifier for the entire duration of the study.

ADMINISTRATIVE ASPECTS

Ethics Committee

The PI will secure approval from the ethics committee for the study protocol, informed consent (IC) form, and other relevant documents before starting the study. Once approved, the IC form cannot be altered without further approval from the ethics committee. The PI is responsible for ensuring that all aspects of the institutional review comply with current regulations. Any modifications to the protocol will undergo the same review and approval process as the original. A progress report will be submitted to the ethics committee at specified intervals, at least annually. Upon the study's completion or termination, the PI will submit a closure letter to the ethics committee.

Economic aspects and insurance coverage

Given the interventional nature of the study, an insurance policy will be provided in addition to that for normal clinical practice.

PUBLICATION OF RESULTS

Upon completion of the study, the results will be the subject of scientific publications.

REFERENCES

1. Loetscher T, Potter KJ, Wong D, das Nair R. Cognitive rehabilitation for attention deficits following stroke. Cochrane Database Syst Rev. (2019) 2019:CD002842. 10.1002/14651858.CD002842.pub3)
2. Nys G.M.S., Van Zandvoort M.J.E., De Kort P.L.M., Van Der Worp H.B., Jansen B.P.W., Algra A., De Haan E.H.F., Kappelle L.J. The prognostic value of domain-specific cognitive abilities in acute first-ever stroke. Neurology. 2005;64:821–827. doi: 10.1212/01.WNL.0000152984.28420.5A.
3. Leśniak M., Bak T., Czepiel W., Seniów J., Członkowska A. Frequency and prognostic value of cognitive disorders in stroke patients. Dement. Geriatr. Cogn. Disord. 2008;26:356–363. doi: 10.1159/000162262.
4. Gottesman R.F., Hillis A.E. Predictors and assessment of cognitive dysfunction resulting from ischaemic stroke. Lancet Neurol. 2010;9:895–905. doi: 10.1016/S1474-4422(10)70164-2.
5. Pendlebury S.T., Rothwell P.M. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: A systematic review and meta-analysis. Lancet Neurol. 2009;8:1006–1018. doi: 10.1016/S1474-4422(09)70236-4.
6. Pollock A., Farmer S.E., Brady M.C., Langhorne P., Mead G.E., Mehrholz J., van Wijck F. Interventions for improving upper limb function after stroke. Cochrane Database Syst. Rev. 2014;2014:CD010820. doi: 10.1002/14651858.CD010820.pub2.
7. Lamb F., Anderson J., Saling M., Dewey H. Predictors of subjective cognitive complaint in postacute older adult stroke patients. Arch. Phys. Med. Rehabil. 2013;94:1747–1752. doi: 10.1016/j.apmr.2013.02.026.
8. Chen C., Leys D., Esquenazi A. The interaction between neuropsychological and motor deficits in patients after stroke. Neurology. 2013;80:S27–S34. doi: 10.1212/WNL.0b013e3182762569
9. Bui KD, Johnson MJ. Robot-based measures of upper limb cognitive-motor interference across the HIV-stroke spectrum. In: IEEE International Conference on Rehabilitation Robotics. (2019) p. 530–5.
10. Adomavičiene A, Daunoravičiene K, Kubilius R, VarŽaityte L, Raistenskis J. Influence of new technologies on post-stroke rehabilitation: a comparison of Armeo spring to the kinect system. Med. (2019) 55:98. 10.3390/medicina55040098.
11. Zengin-Metli D, Ozbudak-Demir S, Eraktas I, Binay-Safer V, Ekiz T. Effects of robot assistive upper extremity rehabilitation on motor and cognitive recovery, the quality of life, and activities of daily living in stroke patients. J Back Musculoskelet Rehabil. (2018) 31:1059–64. 10.3233/BMR-171015
12. Germanotta M, Cortellini L, Insalaco S, Aprile I. Effects of Upper Limb Robot-Assisted Rehabilitation Compared with Conventional Therapy in Patients with Stroke: Preliminary

Results on a Daily Task Assessed Using Motion Analysis. Sensors. 2023; 23(6):3089. https://doi.org/10.3390/s23063089
13. Calabrò RS, Morone G, Naro A, Gandolfi M, Liotti V, D'aurizio C, Straudi S, Focacci A, Pournajaf S, Aprile I, Filoni S, Zanetti C, Leo MR, Tedesco L, Spina V, Chisari C, Taveggia G, Mazzoleni S, Smania N, Paolucci S, Franceschini M, Bonaiuti D. Robot-Assisted Training for Upper Limb in Stroke (ROBOTAS): An Observational, Multicenter Study to Identify Determinants of Efficacy. J Clin Med. 2021 Nov 11;10(22):5245. doi: 10.3390/jcm10225245. PMID: 34830527; PMCID: PMC8622640.
14. Xie H, Li X, Huang W, Yin J, Luo C, Li Z, Dou Z. Effects of robot-assisted task-oriented upper limb motor training on neuroplasticity in stroke patients with different degrees of motor dysfunction: A neuroimaging motor evaluation index. Front Neurosci. 2022 Sep 16;16:957972. doi: 10.3389/fnins.2022.957972. PMID: 36188465; PMCID: PMC9523102.
15. Mehrholz, J., Pollock, A., Pohl, M. et al. Systematic review with network meta-analysis of randomized controlled trials of robotic-assisted arm training for improving activities of daily living and upper limb function after stroke. J NeuroEngineering Rehabil 17, 83 (2020). https://doi.org/10.1186/s12984-020-00715-0
16. Taravati, S., Capaci, K., Uzumcugil, H., & Tanigor, G. (2021). Evaluation of an upper limb robotic rehabilitation program on motor functions, quality of life, cognition, and emotional status in patients with stroke: a randomized controlled study. Neurological Sciences. https://doi.org/10.1007/s10072-021-05431-8.
17. Aprile, I., Guardati, G., Cipollini, V., Papadopoulou, D., Mastrorosa, A., Castelli, L., Monteleone, S., Redolfi, A., Galeri, S., & Germanotta, M. (2020). Robotic Rehabilitation: An Opportunity to Improve Cognitive Functions in Subjects With Stroke. An Explorative Study. Frontiers in Neurology, 11. https://doi.org/10.3389/fneur.2020.588285.
18. Aprile, I., Guardati, G., Cipollini, V., Papadopoulou, D., Monteleone, S., Redolfi, A., Garattini, R., Sacella, G., Noro, F., Galeri, S., Carrozza, M., & Germanotta, M. (2021). Influence of Cognitive Impairment on the Recovery of Subjects with Subacute Stroke Undergoing Upper Limb Robotic Rehabilitation. Brain Sciences, 11. https://doi.org/10.3390/brainsci11050587.
19. Riener R, Lünenburger L, Colombo G. Human-centered robotics applied to gait training and assessment. J Rehabil Res Dev. (2006) 43:679–94. 10.1682/JRRD.2005.02.0046
20. Kiper, P., Richard, M., Stefanutti, F., Pierson-Poinsignon, R., Cacciante, L., Perin, C., Mazzucchelli, M., Viganò, B., & Meroni, R. (2022). Combined Motor and Cognitive Rehabilitation: The Impact on Motor Performance in Patients with Mild Cognitive Impairment. Systematic Review and Meta-Analysis. Journal of Personalized Medicine, 12. https://doi.org/10.3390/jpm12020276.
21. Calabrò RS, Naro A, Russo M, Bramanti P, Carioti L, Balletta T, et al.. Shaping neuroplasticity by using powered exoskeletons in patients with stroke: a randomized clinical trial. J Neuroeng Rehabil. (2018) 15:35. 10.1186/s12984-018-0377-8
22. Metzger JC, Lambercy O, Califfi A, Conti FM, Gassert R. Neurocognitive robot-assisted therapy of hand function. IEEE Trans Haptics. (2014) 7:140–9. 10.1109/TOH.2013.72
23. Manuli, A., Maggio, M., Latella, D., Cannavó, A., Balletta, T., Luca, R., Naro, A., & Calabró, R. (2020). Can robotic gait rehabilitation plus Virtual Reality affect cognitive and behavioural outcomes in patients with chronic stroke? A randomized controlled trial involving three different protocols.. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association, 29 8, 104994 . https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104994.

24. Li, X., Tang, Z., Wu, D., Su, L., Zheng, Y., Chen, P., Zhang, Y., Dou, Z., Li, K., & Hoseinbeyki, A. (2021). Analysis of the Positive Effect of Robot-Assisted Virtual Reality Technology on Rehabilitation of Motor Function and Nerve Function in Cerebral Stroke Patients. J. Medical Imaging Health Informatics, 11, 595-600. https://doi.org/10.1166/jmihi.2021.3372.
25. Hoonhorst MH, Nijland RH, van den Berg JS, Emmelot CH, Kollen BJ, Kwakkel G. How Do Fugl-Meyer Arm Motor Scores Relate to Dexterity According to the Action Research Arm Test at 6 Months Poststroke? Arch Phys Med Rehabil. 2015 Oct;96(10):1845-9. doi: 10.1016/j.apmr.2015.06.009. Epub 2015 Jul 2. PMID: 26143054.
26. Siciliano M, Raimo S, Tufano D, Basile G, Grossi D, Santangelo F, Trojano L, Santangelo G. The Addenbrooke's Cognitive Examination Revised (ACE-R) and its sub-scores: normative values in an Italian population sample. Neurol Sci. 2016 Mar;37(3):385-92. doi: 10.1007/s10072-015-2410-z. Epub 2015 Nov 12. PMID: 26563847.
27. Grant, D. A., & Berg, E. A. (1993). Wisconsin Card Sorting Test (WCST).
28. Guariglia CC. Spatial working memory in Alzheimer's disease: A study using the Corsi block-tapping test. Dement Neuropsychol. 2007 Oct-Dec;1(4):392-395. doi: 10.1590/S1980-57642008DN10400011. PMID: 29213417; PMCID: PMC5619435.
29. Siciliano, M., Chiorri, C., Battini, V., Sant'Elia, V., Altieri, M., Trojano, L., & Santangelo, G. (2019). Regression-based normative data and equivalent scores for Trail Making Test (TMT): an updated Italian normative study. Neurological Sciences, 40, 469-477.
30. Caffarra, P., Vezzadini, G., Dieci, F., Zonato, F., & Venneri, A. (2002). Rey-Osterrieth complex figure: normative values in an Italian population sample. Neurological sciences, 22, 443-447.
31. Nocentini, U., Giordano, A., Vincenzo, S. D., Panella, M., & Pasqualetti, P. (2006). The Symbol Digit Modalities Test--Oral version: Italian normative data. Functional neurology, 21(2), 93-96.
32. Galeoto G, Colalelli F, Massai P, Berardi A, Tofani M, Pierantozzi M, Servadio A, Fabbrini A, Fabbrini G. Quality of life in Parkinson's disease: Italian validation of the Parkinson's Disease Questionnaire (PDQ-39-IT). Neurol Sci. 2018 Nov;39(11):1903-1909. doi: 10.1007/s10072-018-3524-x. Epub 2018 Aug 7. PMID: 30088166.
33. Tedone N, Vizzino C, Meani A, Gallo A, Altieri M, D'Ambrosio A, Pantano P, Piervincenzi C, Tommasin S, De Stefano N, Cortese R, Stromillo ML, Rocca MA; INNI network; Filippi M. The brief repeatable battery of neuropsychological tests (BRB-N) version a: update of Italian normative data from the Italian Neuroimaging Network Initiative (INNI). J Neurol. 2024 Apr;271(4):1813-1823. doi: 10.1007/s00415-023-12108-z. Epub 2023 Dec 7. PMID: 38060030.
34. Solari A, Filippini G, Mendozzi L, Ghezzi A, Cifani S, Barbieri E, Baldini S, Salmaggi A, Mantia LL, Farinotti M, Caputo D, Mosconi P. Validation of Italian multiple sclerosis quality of life 54 questionnaire. J Neurol Neurosurg Psychiatry. 1999 Aug;67(2):158-62. doi: 10.1136/jnnp.67.2.158. PMID: 10406981; PMCID: PMC1736469.
35. Randolph, C., Tierney, M. C., Mohr, E., & Chase, T. N. (1998). The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. Journal of clinical and experimental neuropsychology, 20(3), 310-319.
36. Bull R, Espy KA, Senn TE. A comparison of performance on the Towers of London and Hanoi in young children. J Child Psychol Psychiatry. 2004 May;45(4):743-54. doi: 10.1111/j.1469-7610.2004.00268.x. PMID: 15056306.
37. Posteraro, L., Formis, A., Bidini, C., & Grassi, E. (2004). Aphasia quality of life: reliability of the Italian version of SAQOL-39. European Journal of Physical and Rehabilitation Medicine, 40(4), 257.

38. Moulaei K, Moulaei R, Bahaadinbeigy K. The most used questionnaires for evaluating the usability of robots and smart wearables: A scoping review. Digit Health. 2024 Apr 9;10:20552076241237384. doi: 10.1177/20552076241237384. PMID: 38601185; PMCID: PMC11005511.
39. Bard-Pondarré R, Villepinte C, Roumenoff F, Lebrault H, Bonnyaud C, Pradeau C, Bensmail D, Isner-Horobeti ME, Krasny-Pacini A. Goal Attainment Scaling in rehabilitation: An educational review providing a comprehensive didactical tool box for implementing Goal Attainment Scaling. J Rehabil Med. 2023 Jun 14;55:jrm6498. doi: 10.2340/jrm.v55.6498. PMID: 37317629; PMCID: PMC10301855.
40. Hochleitner, I., Pellicciari, L., Castagnoli, C., Paperini, A., Politi, A. M., Campagnini, S., ... & Cecchi, F. (2023). Intra-and inter-rater reliability of the Italian Fugl-Meyer assessment of upper and lower extremity. Disability and Rehabilitation, 45(18), 2989-2999.
41. Gummesson C, Atroshi I, Ekdahl C. The disabilities of the arm, shoulder and hand (DASH) outcome questionnaire: longitudinal construct validity and measuring self-rated health change after surgery. BMC Musculoskelet Disord. 2003 Jun 16;4:11. doi: 10.1186/1471-2474-4-11. Epub 2003 Jun 16. PMID: 12809562; PMCID: PMC165599.
42. Wang YC, Bohannon RW, Kapellusch J, Garg A, Gershon RC. Dexterity as measured with the 9-Hole Peg Test (9-HPT) across the age span. J Hand Ther. 2015 Jan-Mar;28(1):53-9; quiz 60. doi: 10.1016/j.jht.2014.09.002. Epub 2014 Sep 28. PMID: 25449717.