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Can Eye Tracking Predict Cognitive Function in Neglected Stroke Patients? A Method Proposal

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Abstract

Stroke remains a significant public health challenge in Brazil, leading to permanent motor, functional, and cognitive problems that will impact the quality of life of patients and their families. The comprehensive evaluation of these deficits poses a substantial challenge in rehabilitation, particularly when assessing the interplay between cognitive impairments and motor function. While validated clinical tests exist for individual motor and cognitive assessments, a defined methodology for assessing both domains while performing tasks, such as gaming, with the upper limb affected by stroke, is lacking.

This methodology article aims to demonstrate the feasibility of using the eye-tracking system to map the eye movement of stroke patients during training with an exoskeleton associated with virtual reality gaming. Additionally, it will introduce new technology for cognitive assessment of stroke patients by integrating both systems. The present methodology will include five stroke patients diagnosed at the brain injury outpatient clinic of the Institute of Physical Medicine and Rehabilitation, Clinical Hospital, School of Medicine, University of Sao Paulo (IMREA-HCFMUSP), according to the following criteria: age over 18 years, both genders, clinical and radiological diagnosis (Magnetic Resonance Imaging and/or Computed Tomography) of stroke, right or left hemiparesis. A control group of five healthy subjects will be collected for comparative analysis.

This method will evaluate the feasibility of combining eye-tracking and virtual reality gaming through an exoskeleton to predict cognition in stroke patients. The innovative integration of these technologies offers a promising avenue for advancing our understanding of the complex interactions between motor and cognitive functions in the rehabilitation of stroke survivors.

Introduction

Stroke has been considered one of the biggest public health problems in Brazil, being among the main causes that lead to disability and restrictions in the performance of activities of daily living. Globally, 5 to 10 cases/1000 inhabitants survive stroke, contributing to an escalating prevalence of disability. The number of strokes in third-world countries is more significant than in developed countries. Although the epidemiology of stroke in Brazil is uncertain, Datasus (public health system computing department) registered 160/100.000 inhabitants in 2021, about 978 strokes per day (Cabral et al., 2009).

About 85% of affected individuals remain with functional deficits immediately after brain injury, resulting in partial or total loss of motor function, which may be associated with sensory and cognitive deficits (Abdullah et al., 2011; Lo et al., 2010; Masiero et al., 2011; Norrving & Kissela, 2013; Staubli et al., 2009; Takahashi et al., 2008). In Brazil, it is estimated that after 30 days, 64,4% of the patients are classified Rankin 0 to 2, and 13% Rankin 3 to 5 (Cabral et al., 2009).

Stroke survivors often experience functional limitations in the contralateral upper limb (Levin et al., 2009), impacting daily living and quality of life.

Motor deficits vary based on the stroke-affected brain area, encompassing strength deficits, sensory and cerebellar ataxias, increased spasticity, and

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bradykinesia (Writing Group Members et al., 2010). Quantitatively and qualitatively evaluating the functional motor deficit is a significant challenge in rehabilitation. Quinn et al. (2009) identified 47 assessment instruments described among 126 publications without the existence of a "gold standard" scale (Quinn et al., 2009).

Assessing motor components in stroke patients becomes challenging when non-motor areas are affected. Above all, lesions in areas related to cognitive processing can result in changes that impair motor function, as in the case of agnosia (visual and sensory), apraxia, and heminegligence secondary to injury to the parietal lobe, in addition to hemianopsia secondary to damage to the visual pathways (Foundas, 2013; Lee et al., 2014). Furthermore, the suboptimal performance of the stroke patient in a motor task may be related to deficits in attention, orientation, memory, planning, inhibitory or even motivational control, which may be secondary to injuries in widely distributed neuronal networks, described as subcortical injuries and leukoaraiosis (Douiri et al., 2013; Writing Group Members et al., 2010).

Recently, a study showed that the prevalence of cognitive deficits persists over the years in stroke patients, remaining close to 21% after 14 years of injury, and pointed out the need for health systems to identify and plan more effective actions with this population (Douiri et al., 2013).

Although there are still few studies that discuss the relationship between motor deficits and cognitive limitations in the stroke literature, the significant impact of both on the quality of life of stroke patients and their families is recognized, as well as the importance of evaluating these domains for increasing the success of the rehabilitation program (Verstraeten et al., 2016). However, quantifying the cognitive alterations of the stroke patient is another great challenge.

In clinical practice, we found that such assessments commonly present great difficulty in application due to alterations such as motor deficit and aphasia, which result in the impossibility of accurately assessing the other cognitive domains. Other scales continue to be developed, as recently, in 2015, the Oxford Cognitive Screen scale (Demeyere et al., 2019), in addition to scales that use software, such as the Cambridge Neuropsychological Test Automated Battery (CANTAB Robbins et al., 1994), however, both presenting similar limitations to the previous tests. In an attempt to improve the quality of cognitive assessment, recent studies have used new technologies to assess cognitive and psychiatric alterations, such as eye tracking. This technology allows the measurement of the eye's position (place where the gaze is fixed) and eye movement in a non-invasive way. From the parameters collected through this system, some studies have demonstrated the possibility of obtaining more accurate information about cognitive and emotional processes and sleep alterations (Kinner et al., 2017; Querino et al., 2015; Souza et al., 2013).

Recent research has demonstrated the potential of eye tracking to identify components related to cognitive deficits, hemineglect, and apraxia in stroke patients. Such studies are based on eye movement metrics collected during the performance of motor and cognitive tasks to assess different cognitive outcomes, which are also assessed by applying conventional clinical tests. From the literature, it appears that there is a correlation between the eye-tracking parameters and the clinical tests used. However, more studies are needed to support the use of this technology as a cognitive assessment tool (Cameirão et al., 2016; Kortman & Nicholls, 2016; Lee et al., 2014). However, although eye tracking is a potential device to improve the quality of assessments of some cognitive functions, we find limitations resulting from motor deficits, as mentioned above. Based on our clinical experience, the biggest challenge is assessing motor and cognitive domains while performing tasks with the upper limb affected by stroke. For upper limb rehabilitation, we utilize the Armeo Spring® device, integrating an exoskeleton with virtual reality games, facilitating movement, and providing visual feedback to stroke patients (Kanade et al., 2006; Volpe et al., 2008).

In the case of Armeo Spring®, virtual reality comprises "games" that require greater patient engagement while performing motor tasks with directed functional goals. Such tasks also demand components related to cognitive functions, such as visual-spatial perception, attention, memory, planning, strategy, inhibitory control, picture recognition, and motivation. Thus, cognitive impairment can significantly impact motor performance during training assisted by an exoskeleton associated with virtual reality gaming. As mentioned, quantifying this alteration through traditional scales is not always possible. Furthermore, the literature is unclear about the real impact of cognitive alteration assessed by traditional scales during the performance of motor tasks in naturalistic situations.

Therefore, we propose to employ an eye-tracking system to measure the eye movement of stroke patients during training, assisted by an exoskeleton associated with virtual reality gaming (Armeo Spring® system). We hypothesize that through eye movement analysis, we can infer cognitive changes, such as 1) attention deficits, 2) hemineglect, 3) hemianopsia, 4) apraxia (ideomotor and conceptual/ideational), 5)

planning changes, 6) inhibitory control and 7) visual agnosia, in addition to verifying motivational components. From this analysis, we hope to understand the impact of cognitive impairment during gaming with robotic systems and exoskeletons. Above all, we hypothesized that the association between eye tracking and Armeo Spring® could be proposed as a new cognitive assessment technology, considering the advantages of overcoming the assessment limitation due to motor deficit and quantifying the impact of cognitive impairment more precisely in the performance of activities of daily living.

Methods

The primary aim of this study is to describe in detail the method chosen to evaluate the feasibility of combining eye tracking and virtual reality gaming through exoskeleton (Armeo Spring®) to predict cognitive impairment in stroke patients.

Secondly, the study discusses the main cognitive tests available to evaluate cognitive function after stroke and their limitations.

Participants and Study Design

This transversal controlled study protocol comprises one clinical group (stroke patients and a group of healthy volunteers). Patients admitted to the conventional rehabilitation program of the Institute of Physical Medicine and Rehabilitation (IMREA) will be invited to participate in the study and included after signing the informed consent form previously approved by the Clinical Hospital from the School of Medicine (University of Sao Paulo) Ethics Committee for Research Protocol Analysis CAAE: 80899617.3.0000.0068. For this study, 5 stroke patients who have undergone comprehensive rehabilitation treatment and are currently under regular medical follow-up will be recruited. Patients who agree to participate in the study will undergo a series of assessments at four-time points: 1) Sociodemographic data acquisition; 2) Physical and sensitive evaluation; 3) Traditional cognitive tests 4) Cognitive assessment; Armeo Spring® system and Eye-tracking system.

Sample Size

As a prospective/pilot study, we aim to investigate 5 participants for each group (stroke and health control) to measure statistical significance and power. Further, we aim to explore sample size estimation using GPower3® software.

Inclusion Criteria

Participants of both sexes aged 18 and above, demonstrating and confirming clinical stability through medical evaluation and signing the informed consent form. Stroke group participants must have a clinical and radiological [magnetic resonance imaging (MRI) or computerized tomography] diagnosis of stroke, along with right or left hemiparesis. Specifically, healthy control participants will be included in the study if they present a lack of stroke diagnosis, absence of right or left hemiparesis, and have signed the informed consent form.

Exclusion Criteria

Participants from both groups will be excluded if they have pre-existing bone diseases, joint injuries, motor deficits, and/or severe spasticity joint pain or deformities that affect the limb for performing movements with the Armeo Spring®. Also, they should not present any clinical instability verified in medical evaluation, inability to remain seated in a chair with a backrest during the intervention period (approximately 60 minutes), and other medical and social issues that the medical team deems incompatible with the inclusion of the patient in the protocol.

Sociodemographic data

Sociodemographic data, including date of birth, gender, education, hemispheric dominance, presence of comorbidities, and current medications, will be collected to characterize both the sample and control group. This information will be collected before training/gaming sessions start.

Cognitive and Psychophysiological Assessments

Cognitive Assessments

Regarding the clinical data of the sample, we will collect the clinical history of the injury, including date, injury time, affected hemisphere, and area of the injury, which will also be collected before the start of the training/gaming sessions. Regarding the clinical assessment, we will apply different tests and scales to all patients and control to assess sensitivity, motor function, and cognitive functions. Such tests will be administered one to three days before the training/gaming session (Table 1). All clinical data collected will be used to assess secondary outcomes, and sociodemographic data will be compared to establish a reference of normality concerning the

	Assessment
Motor and Sensory Functional Assessments	Dynamometry (palm grip and forceps). (Mathiowetz et al., 1984)
	Superficial and deep sensitivity of the upper limbs. (Lehman et al., 1993)
	Fugl-Meyer Assessment Upper Limb (FM-UL). (Fugl-Meyer et al., 1975; Michaelsen et al., 2011)
	Modified Ashworth Scale (MAS). (Bohannon & Smith, 1987)
Cognitive Assessments	Catherine Bergego Scale (HAD). (Marques et al., 2019)
	Copy landscape. (Gainotti & Tiacci, 1970)
	Delis Kaplan Executive Functioning System (DKEFS). (Homack et al., 2005)
	Digit Symbol subtest of the Wechsler Adult Intelligence Scale III. (E. D. Nascimento, 2004)
	Montreal CognitiveAssessment (MoCA). (Memória et al., 2013)
	Gap Detection test. (Giannela Samelli & Schochat, 2008)
	Picture Arrangement subtest of Wechsler Adult Intelligence Scale III. (E. D. Nascimento, 2004)
	Picture Completion subtest of Wechsler Adult Intelligence Scale III. (E. D. Nascimento, 2004)
	Stroop Test. (Brandelero & Marco de Toni, 2017)
	Symbol Search subtest of the Wechsler Adult Intelligence ScaleIII. (E. D. Nascimento, 2004)
	Tasks to cancel lines, stars, bells and line bisections. (Gauthier et al., 1989; Schenkenberg et al., 1980)
	Trail Making Tests. (Hamdan & Hamdan, 2009)

Table 1: *Assessment instruments used for Motor/Sensory and Cognitive measurement.*

control group.

As previously mentioned, knowing the patients' cognitive aspects during the study is of paramount importance, both to quantify more precisely the impact of the cognitive alteration on the performance of activities of daily living and to compare these already validated data with the results obtained by Eye Tracking.

For this purpose, a battery of cognitive tests and an instrument for investigating emotional aspects were chosen based on the literature and focusing on our research objective.

For the cognitive assessment of stroke patients, the National Institute of Neurological Disorders and Stroke (NINDS) recommends the following tests: Montreal Cognitive Assessment (MoCA), Delis Kaplan Executive Functioning System (DKEFS)-Trail Making Tests, Digit Symbol subtest of the Wechsler Adult Intelligence Scale III, Symbol Search subtest of the Wechsler Adult Intelligence Scale III, Stroop Test, Hopkins Verbal Learning Test-Revised, Rey-Osterrieth Complex Figure Copy and Delay, Boston Naming Test (BNT) 30-item version, Information Questionnaire for Cognitive Decline (IQCODE), Neuropsychiatric Inventory (NPI) Questionnaire.

Regarding cognitive assessment, in a study, Verdon et al. (2010) used a systematic battery of tests to assess aspects of extrapersonal neglect and different perceptual, attentional, and visual-motor domains. In this study, they used tests such as canceling bells, copying the landscape (patients were invited to copy a drawing made up of five elements arranged on an A4 sheet), cutting lines, reading text (specific to the clinic where the study took place), reading compound words and gap detection test.

However, due to our number of patients with physical and motor disabilities, some tests were replaced to better suit the study population. The following were chosen for this purpose:

Hospital Anxiety and Depression Scale (HADS): is a scale that assesses the tendency to symptoms of anxiety and/or depression (Botega et al., 1995).

Montreal Cognitive Assessment (MoCA): the MoCA instrument is a screening tool for assessing possible mild cognitive dysfunctions. It investigates cognitive domains such as attention and concentration, executive functions, memory, language, visuo-constructive skills, conceptualization, calculation, and orientation. (Nasreddine et al., 2005).

Trail Making Tests: was used qualitatively. It is an instrument that primarily assesses the selective attention function (but it can also access the areas of cognitive flexibility, processing speed, visual tracking, and inhibition of specific responses to the detriment of others). It is subdivided into two independent parts (A and B), in which in part A, the examinee must draw a line going from one number to the other, in ascending sequence, in the shortest possible time. In part B, the examinee must draw a line in ascending order but alternating between a number and a letter in the shortest possible time (Hamdan & Hamdan, 2009).

Digit Symbol of the Wechsler Adult Intelligence Scale III (WAIS-III): is a sub-test of the intelligence assessment battery that primarily assesses attention. These are two tasks that are applied independently of each other: Direct Order and Inverse Order. In both tasks, a series of sequence numbers is read aloud

to the participant. In each item of the Direct Order, the participant must repeat the numerical sequence in the same order presented. In Reverse Order, the participant must repeat the numerical sequence in the opposite order to that presented by the researcher (that is, backward) (E. do Nascimento & Figueiredo, 2002).

Completing figures from the Wechsler Adult Intelligence Scale III (WAIS-III): it is also a sub-test of the intelligence assessment battery that primarily assesses visual perception. Several figures are presented individually, and the participant must point to and/or name the central part missing from the figure (E. do Nascimento & Figueiredo, 2002).

Arrangement of figures from the Wechsler Adult Intelligence Scale III (WAIS-III): primarily assesses organization, planning, and executive functions. It is a set of illustrated cards that the participant must organize to create a story with logic within a specific time limit (E. do Nascimento & Figueiredo, 2002).

Stroop Test: the examinee must primarily identify colors and words in three different tasks: reading words, naming colors, and identifying the color in which each word is written, to the detriment of the color in which each word is written (the words are a different color concerning the color in which it is written), in the shortest possible time (Brandelero & Marco de Toni, 2017).

Bell Cancellation Test (TCS) is a neuropsychological tool for canceling targets (bells) between distractors. That is, the examinee must identify the bell figures among other figures present on the same sheet. Assesses focused and selective attention, visual perception, praxis, processing speed, and some components of executive functions (planning and cognitive efficiency). In addition, it may be sensitive to detect mild to moderate signs of visual hemineglect (Gauthier et al., 1989). Catherine Bergego Scale (CBS): this scale aims to analyze the examinee's functionality, in which questions are asked about the participant's daily situations to assess the presence of unilateral spatial neglect (Marques et al., 2019). BIT (Behavioral Inattention Test): is a test made up of six conventional sub-tests (drawing, copying, drawing, and identifying specific figures) and nine behavioral sub-tests, which assess aspects of the examinee's daily life, in which the possibility of one-sided spatial neglect (Hartman-Maeir & Katz, 1995). For this research, we qualitatively used only the conventional sub-tests.

Gap Detection Test (GDT): was used qualitatively. The participant is asked to mark all circles with a gap (either on the left or right side of the circle) between other circles without a gap. The possibility of egocentric neglect (omission of targets on the left side of the sheet) and allocentric neglect (omission of targets with a gap on the left side) is investigated (Giannela Samelli & Schochat, 2008).

Armeo Spring®

A training/gaming day will be held with Armeo Spring® and associated with eye tracking, lasting approximately 30 minutes. As mentioned earlier, the Armeo Spring® is an upper limb exoskeleton associated with virtual reality. Thus, the patient must be in a common chair to view the monitor. Subsequently, the affected upper limb will be positioned on the exoskeleton with the help of a therapist. During the positioning of the upper limb, the therapist evaluates and conducts all necessary adjustments to the device to promote the ideal functional position for the performance of the tasks. After the adjustments, the therapist starts registering the patient in the system and calibrates the three-dimensional workspace according to the active movement presented by the patient.

This entire procedure is part of the evaluation routine before the training protocol assisted by the exoskeleton associated with virtual reality gaming. It allows for system configuration according to the user's profile. System calibration will be performed without eye tracking to ensure the patient's adaptation and habituation to the device. During this initial period, the presence of joint pain, spasticity, synergisms, muscle contractures, or deformities that may compromise the positioning and movement of the upper limb during task performance will be evaluated. The patient may be excluded from the study if such aspects are identified during this adaptation.

Then, eye tracking will be positioned and calibrated for the patient using glasses adapted to the system. Two "virtual games" already existing in the Armeo Control® software, version 2.2.0.30, will be pre-selected for this protocol. They are: "Rain Mug" and "Balloon". The "Rain Mug" collects the drops, moving a bucket from side to side. The "Balloon" aims to pop the balloons all over the screen, deflecting the bombs and ducks that appear eventually. Each game will last 3 minutes per session and has the same scene sequel, enabling good task control for evaluation. The session's total time is 12 minutes of training, and the upper limbs will be tested bilaterally as a comparison.

Eye Tracking system

The SMI Eye Tracking glasses are an eye tracking system equipped with an HD camera (1280x960 pixels) to capture the environment observed by the participant, with automatic adjustment for light. In ad-

dition, two other cameras have diodes that emit infrared rays (Near Infrared Light-Emitting Diodes. NIR-LEDs). Infrared light, upon reaching the retina and passing through the cornea, generates a corneal reflex that is captured by the built-in camcorders. The reflection improves the pupil's illumination, facilitating the video camera's recording and reflecting the light towards the computer screen (pupil center corneal reflection PCCR), whose coordinates are also recorded by the video at 60 Hz.

The camera images and coordinates are computed, and the ocular tracing record is reconstructed from the result. The error range is 0.63 cm, making it possible to move the head 7.6 cm to the sides, 6.4 cm back and forth, and 5.1 cm up and down. All data the system captures are transmitted online to an exclusive smartphone device for storing information. The data generated by the device provides information regarding the 3D location of the eyes (including whether it is within range of the device), the x and y coordinates of the eye recorded on the monitor, pupil diameter, fixation analysis, and saccadic movements. Data can be exported in Excel files, in real-time in AVI files, or as hotspot-type images.

Feasibility Analysis

To assess the primary outcome, where we intend to demonstrate the feasibility of using the eye-tracking system for mapping the eye movement of stroke patients during training/gaming with Armeo Spring®, we will take the measures described below. The measure could bring information on: the number and time of fixations at each area of the screen, which we believe would be different in patients with hemianopsia or hemineglect; number and time of fixations outside the screen and heat maps, that could suggest attention deficits and difficulties at abstraction; lateral and vertical movements, that could be distorted on patients with different cognitive impairments, as hemineglect, hemianopsia, attention deficits and difficulties at abstraction and planning.

First, we will investigate the time to adjust and calibrate the equipment during patient positioning. This is an important measure to differentiate the time between preparation and the assessment and estimate the average time needed to conduct this new assessment methodology. In order to quantify the time required for adjustment and calibration of the equipment, we will film the training/gaming sessions for later visualization and measurement (Zariffa et al., 2012).

Also, concerning feasibility, we must consider both the therapist's and the patient's perception of the combined use of eye-tracking and Armeo Spring® systems. For this purpose, we will apply questionnaires after the end of the session to collect information about the use of the systems for evaluation. The questionnaires will be structured, including questions that can be answered according to a graduated scale from 1 to 10, with 1 being "strongly disagree" and 10 "strongly agree". The questionnaires will be applied at the end of the training/gaming sessions (Zariffa et al., 2012).

Statistical Analysis

Initially, participants will be analyzed to study the distribution of socio-demographic data, information about the history of the disease, and other clinical information. For this analysis, we will use descriptive statistics to characterize the baseline of the sample.

To analyze the primary outcome, descriptive statistics will be applied to the variables' time spent to adjust and calibrate the questionnaire's equipment results on the perception of patients and therapists. The results will be analyzed and later presented in the table. Regarding eye movements, the data obtained by using eye tracking will be recorded from the beginning of each activity with Armeo Spring®. The areas of interest (AOI) will be the switch screen on which the virtual games will be presented (target and related distractions), as well as the environment around the computer screen (unrelated distractions). Fixations will be counted for each object type. The eye-tracking data will be processed to generate the cognitive activity index (using data on pupil dilation), heat maps, and the scan path, thus enabling qualitative analysis.

The information obtained by eye tracking from both groups will be analyzed using a histogram to verify the normal data distribution. The Wilcoxon-Mann-Whitney test or T test for non-parametric or parametric data will be used to compare the results of patients with the control group. Pearson or Spearman correlation tests and parametric or non-parametric data will be used to analyze the correlation of eye-tracking data with clinical data.

Considering the two "virtual games" played in the Armeo Control® software ("Rain Mug" and "Balloon"), we will evaluate the performance of the patient/participant at the end of the task, considering the measures of i) accuracy, ii) number of errors; iii) total task time. As we will do for the measures obtained with the eye-tracking system, we will use these measures obtained with the games to compare the groups.

Finally, although the analyses described above contribute to the objective of the work, all the measures

described will be evaluated in association with the cognitive measures. Thus, to test such associations, we will perform statistical analysis using STATA® 17.0. For these cross-sectional analyses, the cognitive measures' final game score will be considered dependent variables, and the data from eye-tracking and the virtual reality game will be considered independent variables. It is worth mentioning that all variables chosen for the univariate analysis will be selected and chosen based on biological relevance/plausibility. Thus, only the variables supported by previous stroke-related literature will be analyzed.

Next, we will initially run linear univariate analysis to reveal which independent variables have a significant relationship with the dependent variables to determine the values of the unadjusted β coefficients and their 95% confidence intervals (CI). Next, we will build the models for the linear multivariate analyses, following the purposeful selection of variables approach (Bursac et al., 2008), where we combined theoretical relevance, confounding assessment (based on the literature and changes or more than 10% in the β coefficients), and statistical criteria (variables that had a p-value <0.2 in the univariate analyses), thus the inclusion of potential confounding factors that did not reach the significance level of 0.05. Variables that did not maintain statistical significance will be excluded from one of the models (backward stepwise regression). This method is typically adopted based on the validity of this procedure in its ability to avoid suppressor effects (Hocking, 1976). In order to guarantee the statistical quality of the models presented here, the four assumptions defended by Osborne and Waters (Osbourne & Waters, 2002) will be reviewed, namely Linearity, Homoscedasticity, Independence, and Normality. Finally, it is worth mentioning that, in order to control the model for any confounder, we will test by age, sex, education, and motor measures (Dynamometry, Superficial and deep sensitivity of the upper limbs, Fugl-Meyer Assessment Upper Limb and Modified Ashworth Scale).

Discussion

This methodological article evaluates the association between cognitive measures and the joint application of the eye-tracking system assisted by an exoskeleton associated with virtual reality gaming (Armeo Spring® system) in stroke patients. We hypothesize that through eye movement analysis, we can infer cognitive changes, such as 1) attention deficits, 2) hemineglect, 3) hemianopsia, 4) apraxia (ideomotor and conceptual/ideational), 5) planning changes, 6) inhibitory control and 7) visual agnosia, in addition to verifying motivational components. From this analysis, we hope to understand the impact of cognitive impairment during training with robotic systems and exoskeleton gaming.

Based on the reviewed literature and our clinical practice, we believe that the measurements obtained by associating eye tracking and the exoskeleton associated with virtual reality training/gaming will make evaluating the cognitive aspects presented above possible without using classical instruments. It is important to emphasize that the intention of the present method is not to replace such instruments, which have broad application and good accuracy in the evaluations, but rather to evaluate the feasibility of a diagnostic alternative since, in many cases, stroke patients do not have adequate movement of hands. Therefore, the traditional assessment may become unfeasible.

The only study that combines ET and virtual reality analyzed eighteen stroke patients with spatial neglect wearing VR headsets. They should look around freely in a symmetric 3D museum scene with three pictures (Hougaard et al., 2021; Kaiser et al., 2022). It was susceptible to detect egocentric neglect and caputomotor neglect. Otherwise, allocentric neglect and oculomotor neglect were not.

Our proposal includes a more controlled task, which we believe could bring more sensibility to detect all kinds of neglect. As the Armeo Spring® system is applied on a computer, the gaze asymmetry between the sides of the scream could detect allocentric neglect. The oculomotor neglect could be inferred as we analyze head movement to compensate for the difficulty of visualizing one side of the scream.

Beyond that, fixations outside the area of interest and the game punctuation could bring information about attentional deficits, planning changes, and inhibitory control.

It is expected that the results of this study will allow us, in the near future, to apply new perspectives to the area of rehabilitation within the methodology based on scientific evidence, especially concerning the assessment of cognitive functions. As mentioned above, eye tracking is a non-invasive technology in which a sensor allows you to record accurate eye position and movement measurements.

Feasibility

The primary challenge of this method is precisely in the proposed objective, which is to evaluate how feasible the application of this method is. Despite being simple to assemble, apply, and analyze the data, we sought a method that could be complex to provide

accurate information and be associated with classic cognitive assessment measures but simultaneously be simple to use in the clinical practice of rehabilitation centers. Taking the eye tracking system as an example, currently, some groups have been developing increasingly accurate systems with high sample rates, but with a high cost and also the need, for example, to fix the head of the evaluated individual to guarantee the accuracy of the data. On the other hand, other groups have been developing cheaper systems that are more adaptable to different contexts but with reduced accuracy. In this sense, the method proposed here will use an eye tracking system with glasses precisely to facilitate its use, guaranteeing good quality and accurate data with a 60hz sample rate system.

In any case, we expect the following challenges: i) motor impairment of the arms more significant than necessary to perform the training/gaming with the exoskeleton; ii) some stroke patients, with greater negligence, will present greater visual compensation with head movement; iii) capture of pupillary information can be compromised by the incidence of light in environments and injures of cranial nerve, as ptosis or lack of eye movement.

Among the measures collected for the analysis, we will consider these three points in the final assessment of the feasibility of the method.

Gamification and Health Promotion

Two additional crucial aspects of the present method include the playful nature of game evaluations and the broader impact of measuring cognition through a game on health promotion. Gamification significantly measures cognition and emotions (Mullins & Sabherwal, 2020; Sardi et al., 2017). Typically, the playful character of the activity not only allows the player to be motivated by the task, increasing their availability to continue the training/game, but also generates emotion modulation, promoting an increase in positive emotions (Boyle et al., 2012; Hemenover & Bowman, 2018). This aspect is of significant importance, especially for the population in question here, in which stroke patients often present negative affect and mood (Mitchell et al., 2017). Thus, it is possible to extrapolate the objectives of the present method, pointing out the possibility of the training proposed here, in addition to providing a significant association with cognition measures, allowing a positive emotional impact for the patient.

Thus, considering the promotion of health and the well-being of this population of patients undergoing rehabilitation, an instrument that, in addition to not causing boredom and tiring the patient, can provide essential measures of the patient's state of cognition, at the same time as promotes momentary well-being and the emotional health of this patient, is of scientific and public health relevance. Also, the game allows greater control of the presented stimuli and interpatient standardization.

Ethical statement

Finally, regarding implementing a new method, all patients must obtain approval from the responsible physician to participate in the study. Each patient's participation is subject to the signing of the Informed Consent Form previously approved by the Research Ethics Committee – of HC FMUSP. To verify the feasibility of using the eye tracking system to map the eye movement of stroke patients during training/gaming with Armeo Spring®, the data collected through the questionnaires will be submitted for appropriate statistical analysis. The other data collected by applying clinical tests will also be submitted for statistical analysis to verify secondary outcomes. In this phase, a patient database will be created with the following objectives: 1) to preserve the confidentiality of patient data and 2) to allow the exchange of information between researchers.

According to previous publications, eye tracking uses glasses and does not pose risks to the patient. Regarding Armeo Spring®, there are also no reports of risks to patients. Comprehensively, robot or exoskeleton-assisted therapy has been used in several research centers with 100% safety record, according to reports in the literature (Kanade et al., 2006; Volpe et al., 2008). Therefore, harmful effects on patients are not expected due to the non-invasive characteristics of both systems. However, if harmful effects occur, IMREA-HCFMUSP has a team of physicians and nurses to assist patients with their clinical and functional needs.

Author Contributions

MS conceived the initial idea in this study protocol, MS and LB designed the study, and MS, NA, LM, and FF drafted the manuscript article. All authors reviewed and approved the final version of the paper.

Statement of Ethics

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Conflicts of Interest

The authors declare no conflict of interest.

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