

**UNIVERSIDAD FRANCISCO DE VITORIA**  
**ESCUELA INTERNACIONAL DE DOCTORADO**  
Doctorado en Biotecnología, Medicina y Ciencias Biosanitarias



**TESIS DOCTORAL**

**DESIGN, DEVELOPMENT AND  
VALIDATION OF A NEW MEDICAL  
DEVICE FOR HAND MOTOR AND  
COGNITIVE EVALUATION AND  
REHABILITATION**

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Madrid, Octubre 2024

# Agradecimientos

Quiero expresar mi más sincero agradecimiento a la Universidad Francisco de Vitoria y a la Escuela Internacional de Doctorado por brindarme la oportunidad de desarrollar esta investigación.

A mis directores de tesis, gracias por vuestra ayuda y apoyo incondicional a lo largo de todo este proceso. Vuestra cercanía y comprensión hicieron fácil lo difícil, y por ello, os estoy profundamente agradecida.

En especial, a mi co-director de tesis, el Dr. Juan Pablo Romero: gracias por tu paciencia, guía y sabiduría en cada etapa de esta tesis. Aprecio enormemente la confianza y el apoyo que me brindaste desde el primer momento, haciéndome sentir parte del equipo y del hospital como una más.

A mi co-directora de tesis, la Dra. Carmen Sánchez: gracias por ofrecerme esta increíble oportunidad; sin ti, no habría conocido a Juan Pablo ni al equipo GINDAT, y esta tesis no hubiese sido posible.

Agradezco también al equipo de investigación GINDAT, por su colaboración y apoyo, y por la acogida en el equipo a pesar de mi formación y experiencia tan distintas. En especial, a Aída, Fran, Yeray y Marcos, gracias por todo el conocimiento que me habéis compartido y por vuestra visión del mundo clínico. Gracias a vosotros pude cumplir el sueño de trabajar en el hospital y aprender directamente de los pacientes, una experiencia que me aportó mucho más de lo que imaginaba. Y a Mercedes, por su apoyo como otra ingeniera doctoranda algo más veterana, gracias por todos tus consejos y apoyo.

Gracias también a todos los pacientes que conocí durante las investigaciones en el Hospital de la Beata, y a todos los voluntarios que hicieron posible la validación de este proyecto: vecinos, antiguos compañeros y profesores de la UPM, alumnos de la UFV, etc.

No puedo dejar de agradecer a los compañeros del Centro de Automática y Robótica del CSIC, en especial a Gabriel. Sin vosotros, Amber no sería lo que es hoy.

Y, por supuesto, a mi familia, quienes siempre creyeron en mí y me apoyaron sin reservas. A mis padres, Aurora y Antonio, gracias por inculcarme la pasión por el conocimiento, el esfuerzo y la superación, y por enseñarme que todos los problemas, de una forma u otra, tienen solución. Gracias, mamá, porque sé que, aunque no lo seas en papel, llevas una ingeniera dentro de ti que, indirectamente, me impulsa cada día a ser mejor en mi profesión. Gracias, papá, porque descubrí el mundo de la Ingeniería Biomédica gracias a ti y a tu constante apoyo en mis decisiones (nadie como vosotros sabe lo difícil que me resulta a veces decidirme). Y a Álex, por estar siempre a mi lado, en los buenos y en los malos momentos, gracias por mover cielo y tierra cuando era necesario y por tu paciencia (casi) infinita. Tus inquietudes y ganas de superación y éxito me motivan a superarme cada día. A los tres, nunca podré agradecerlos lo suficiente todo lo que me habéis aportado. Gracias por estar siempre ahí, por acompañarme y, sobre todo, por aguantarme en toda esta etapa.

Sin el apoyo de todos vosotros, esta tesis no habría sido posible. Gracias, de corazón.

# Abstract

Stroke is a leading cause of disability in adults worldwide, with most patients experiencing some degree of chronic motor and cognitive disability that prevents them from performing certain activities of daily living. Rehabilitation should begin as soon as possible, with multidisciplinary evaluations and training where motor rehabilitation and cognitive approaches stand out. Traditionally, post-stroke rehabilitation strategies have been implemented separately in terms of motor and cognitive functions. However, recent studies show that hand motor interventions can have a positive impact on cognitive recovery.

This thesis presents AMBER (Portable and Modular device for comprehensive Brain Evaluation and Rehabilitation), an innovative medical device designed to support the cognitive and motor evaluation and rehabilitation of the hand. AMBER is a simple, portable, ergonomic, and affordable device based on LED lights and force-sensitive resistors, in which each finger interaction is recorded to provide information on finger strength, processing speed, and visual memory.

This work focuses on the design, development, and validation of AMBER. The design relies on findings obtained through a systematic review, which suggests that integrating strength assisted training with conventional rehabilitation methods can significantly improve global cognition in stroke patients. Additionally, AMBER's design and task set, inspired by established physical and neuropsychological assessments, offer a modernized approach to measuring key motor and cognitive variables.

Through a series of validation studies involving healthy volunteers and focus groups with stroke rehabilitation specialists, this work also evaluates the effectiveness and usability of AMBER. The device's adaptability and positive reception from both therapists and healthy volunteers suggest its potential usefulness in a spectrum of neurological conditions beyond stroke, including motor-impairing diseases such as peripheral neuropathies and rheumatic pathologies, and other cognitive pathologies such as vascular or neurodegenerative mild cognitive impairment. However, comments have pointed out areas for improvement oriented toward enhanced ergonomic and functional usefulness, which will guide AMBER towards new research lines and prepare it to be used in formal clinical trials with patients. These innovative characteristics have led to a request for an international patent for AMBER.

In conclusion, AMBER represents an important step forward in the field of post-stroke rehabilitation, incorporating the principles of cognitive-motor interdependence and suggesting broad applications for a variety of other pathologies beyond its initial post-stroke focus. By facilitating early, integrated, patient-centered rehabilitation, AMBER promises to redefine the recovery process for stroke survivors, providing information on more effective rehabilitation strategies and highlighting the critical role of innovative technologies in advancing patient care.

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# Acronyms

<b>ACA</b>	anterior cerebral artery
<b>ADL</b>	Activities of Daily Living
<b>ATP</b>	adenosine triphosphate
<b>BBB</b>	blood–brain barrier
<b>BBT</b>	Box and Blocks Test
<b>CBT</b>	Corsi Block-Tapping
<b>CI</b>	confidence interval
<b>DSCT</b>	Digit Symbol Coding Test
<b>EM</b>	Evaluation Mode
<b>EMG</b>	Electromyography
<b>FR</b>	Functional Requirement
<b>FSR</b>	Force Sensitive Resistor
<b>FMUE</b>	Fugl-Meyer Upper Extremity scale
<b>HRD</b>	Hand Rehabilitation Device
<b>HTML</b>	HyperText Markup Language
<b>ICH</b>	intracerebral hemorrhage
<b>ICC</b>	Intraclass Correlation Coefficient
<b>LED</b>	Light-emitting diode
<b>LL</b>	Lower Limbs
<b>MAS</b>	Modified Ashworth Scale
<b>MCA</b>	middle cerebral artery
<b>MD</b>	mean difference
<b>MI</b>	Motricity Index
<b>MMSE</b>	Mini Mental State Exam

<b>MoCA</b>	Montreal Cognitive Assessment scale
<b>NFR</b>	Non-Functional Requirement
<b>NMA</b>	Network Meta-Analysis
<b>NSA</b>	Nottingham Sensory Assessment
<b>PCA</b>	posterior cerebral artery
<b>PHP</b>	Hypertext Preprocessor
<b>RCT</b>	randomized control trial
<b>RHB</b>	Rehabilitation
<b>RoB</b>	risk-of-bias
<b>RT</b>	reaction time
<b>SD</b>	standard deviation
<b>SDMT</b>	Symbol Digit Modality Test
<b>SEM</b>	standard error of measurement
<b>SUCRA</b>	surface under the cumulative ranking curve
<b>TIA</b>	transient ischemic attack
<b>TM</b>	Training Mode
<b>TMT</b>	Trial Making Test
<b>TMT-A</b>	Trial Making Test Part A
<b>TMT-B</b>	Trial Making Test Part B
<b>t-PA</b>	tissue plasminogen activator
<b>UL</b>	Upper Limbs
<b>VR</b>	Virtual Reality
<b>WAIS</b>	Wechsler Adult Intelligence Scale

# 1. Introduction

## 1.1 Stroke

Stroke can be defined as a cerebrovascular disorder caused by hypoperfusion or decreased cerebral blood flow, which temporarily or permanently alters the functioning of one or more parts of the brain.

Stroke is the second most common cause of death in Europe and the world, and a leading cause of adult disability [1, 2]. The incidence of stroke increases with age, with a greater population affected among men, except for ages above 85 years old [3]. Currently, there are around 12.2 million new cases of stroke each year worldwide, with a prevalence of 143 million [4]. By 2035, the incidence of stroke is expected to increase by 34% [5]. In Europe, it is responsible for 9% of all deaths in men and 13% in women [6]. Among the survivors, most experience some degree of both motor and cognitive chronic impairment, which makes them unable to carry out certain Activities of Daily Living (ADLs) [7].

### 1.1.1 Pathophysiology of stroke

There are two main types of stroke depending on the nature of the injury: ischemic stroke and hemorrhagic stroke, which represent around 87% and 13% of stroke cases, respectively [8]. The type of stroke especially conditions its management during the acute phase and also its treatment [3]. However, subsequent rehabilitation will depend on the clinical manifestations presented by the patient. These clinical manifestations depend on the characteristics, duration and location of the ischemia [9]. It is generally characterized by a focal neurological deficit with an abrupt onset. In the case of large vessel occlusion, symptoms vary depending on the affected artery, being the most common the following: hemiparesis, hemiplegia, hemianesthesia, hemianopia, apraxia, dysarthria, dysphagia, dysphasia, memory disorders and aphasia [9]. In cases of stroke due to small vessel occlusion, the most frequent syndromes are: pure motor syndrome (facio-brachio-crural paresthesia of a hemibody), pure sensory syndrome (hypoesthesia or facio-brachio-crural paresthesia), sensory-motor syndrome (paresis with hypoesthesia), dysarthria with clumsy hand and hemiparesis with hemiataxia [10].

The lack of blood supply and, therefore, oxygen and glucose in an area of the brain triggers tissue necrosis in that region [11]. This decrease in the level of oxygen and glucose

results in a decrease in the energy available in brain cells to carry out different cellular functions. Specifically, neurons lose their ability to maintain the transmembrane ionic gradient necessary for homeostasis, leading to excessive neuronal depolarization and an increase in the release of excitatory neurotransmitters and pro-inflammatory molecules [9]. As a consequence, accumulations of  $\text{Ca}^{2+}$  and  $\text{Na}^+$  ions are produced, and the signaling pathways are altered, thus activating catabolic processes mediated by proteases, lipases and nucleases that interrupt neuronal function and induce cell death [12]. It is postulated that the first cause of cell death could be due to the accumulation of intramitochondrial  $\text{Ca}^{2+}$ , which reduces adenosine triphosphate (ATP) synthesis [9]. In addition, after the interruption of blood flow, the reperfusion of the damaged tissue can trigger an inflammatory and immune response that causes an increase in the permeability of the blood-brain barrier (BBB), producing cerebral edema [9].

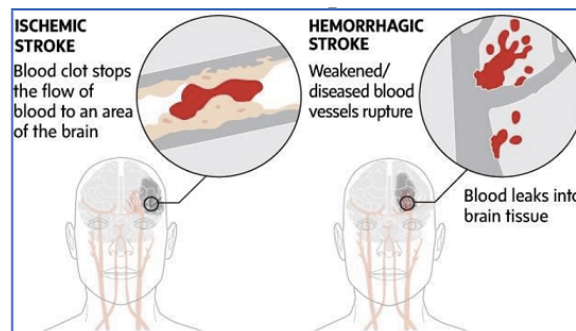


Figure 1.1: Types of stroke: Ischemic and Hemorrhagic [13].

The following sections explain the pathophysiology of the different types and subtypes of stroke.

#### 1.1.1.1 Ischemic stroke

Ischemic stroke is characterized by alterations in the brain blood supply caused by partial or total occlusion of a cerebral blood vessel, with the main consequence of lack of oxygenation or anoxia [9]. There are three main types of brain ischemia: thrombosis, caused by a local obstruction of a blood vessel due to a disorder of its wall; embolism, when the obstruction is caused by a particle originated in other region which travels to a brain blood vessel; and systemic hypoperfusion, when is a problem of low blood flow in the brain due to circulatory failure due to the lack of pumping of the heart (heart attack) [14].

Brain ischemia can lead to focal cerebral ischemia, if only one area of the brain has been affected, or global cerebral ischemia, if the interruption of blood flow has affected the entire brain [15]. It is also important to distinguish whether the occlusion is produced in a capillary of the brain or if it occurs in a large blood vessel, which represents 80% and 20% of ischemic stroke cases respectively [16].

#### Focal Cerebral Ischemia

In focal cerebral ischemia, there is a reduction or interruption of blood flow in a certain area of the brain as a consequence of the occlusion of an artery [17]. This reduction in

blood flow produces a decrease in the supply of oxygen and glucose, with the consequent decrease in energy, causing the loss of function of cell membranes and ionic homeostasis. This causes different functional alterations in the brain tissue, reaching necrosis if the flow is completely interrupted [11]. The clinical manifestations will depend on the affected artery and the extent of the injured tissue [18]. Below, a figure with the main cerebral arteries is shown and the symptoms associated with a stroke in the most important ones are described.

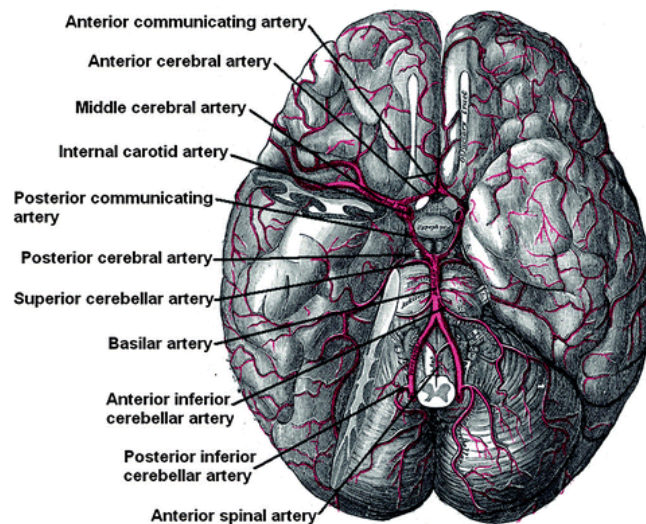


Figure 1.2: Vascular anatomy of the brain [19].

- **The middle cerebral artery (MCA)** is one of the major cerebral arteries and the most common involved in stroke. The MCA is located in the lateral sulcus between the frontal and temporal lobes. It supplies a large area of the lateral cerebral surface and part of the basal ganglia and the internal capsule via four segments (M1, M2, M3, and M4). As it mainly supplies the somatosensory cortex, the symptoms associated with a stroke in MCA are related to motor and sensory alterations that mainly affect the face and upper extremities: contralateral hemiparesis, facial paralysis and sensory loss in the face and upper limbs. Additionally, there may be symptoms such as dysarthria, neglect, and aphasia [20].
- **The anterior cerebral artery (ACA)** provides blood supply to the frontal, prefrontal, primary sensory, primary motor, and supplemental motor cortices. The sensory and motor cortices receive sensory information and control movement of the contralateral lower extremity. The supplemental motor area contains the Broca's area, which is involved in the initiation of speech. The prefrontal cortex is used to organize and plan complex behavior and is thought to influence the personality. For this reason, the most frequent symptoms of an ACA infarction are contralateral sensory and motor deficits in the lower extremity, preserving the correct activity of the face and upper limbs [20].
- **Posterior cerebral artery (PCA)** is divided into the superficial PCA and the deep branches, which supply the occipital lobe, the inferior portion of the

temporal lobe, the thalamus and other deep structures of the brain respectively. The occipital lobe is the location of the primary and secondary visual areas, where sensory input from the eyes is interpreted. The thalamus relays information between the ascending and descending neurons, while the internal capsule contains the descending fibers of the lateral and ventral corticospinal tracts. If the infarction occurs in the deep branches of the PCA, symptoms may include hypersomnolence, cognitive deficits, ocular disturbances, hypoesthesia, ataxia, and even hemisensory loss and hemiparesis. In the case of superficial PCA infarction, the symptoms are related to visual and somatosensory deficits, such as alterations in tactile sensation and proprioception [20].

Within focal cerebral ischemia, two types of stroke can be distinguished depending on the duration of the occlusion: transient ischemic attack (TIA) and cerebral infarction.

- **Transient ischemic attack** or **TIA** is defined as an episode of focal neurological dysfunction lasting less than 24 hours [21, 22]. Of the total number of strokes that take place in Spain, TIAs correspond to 16.4% of cases [3]. Furthermore, the physiology, prognosis, and treatment of TIA vary greatly depending on the brain area affected, on which the clinical manifestations also depend. The TIA is especially important as a predictor of stroke: TIA patients are around 10% more likely to suffer a stroke during the subsequent 90 days, with half of them happening the following week. During the 5 years after TIA, studies show a stroke incidence of 30% [21, 22].
- **Cerebral infarction** occurs when blood flow to an area of the brain is interrupted for more than 24 hours. This produces tissue necrosis in the affected brain region [15], area also known as the infarct core [9]. Around the infarcted area there may be residual blood flow and a minimal metabolic activity sufficient to maintain cell viability for a certain time (until the production of ATP falls below 50% of normal levels, triggering death cell by apoptosis [23]), although without preserving its normal function. This area around, called penumbra, although it is at risk of cell death, is capable of recovering its original state if blood flow is restored, thus being the focus of treatments to reduce injury and sequelae after cerebral infarction [24–26].

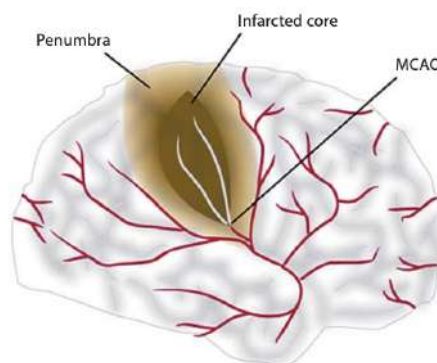


Figure 1.3: Infarcted nucleus within the immediate area of the occluded artery, followed by a penumbra, in cerebral ischemia [27].

## Global Cerebral Ischemia

On the other hand, in the case of global cerebral ischemia the decrease or interruption of blood flow simultaneously affects the entire brain, mainly border zones between the main arteries territory. It occurs commonly in patients which cardiac arrest or undergoing complex cardiac surgery. Its neurologic sequelae include coma, seizures, ischemic stroke, delirium, and neurocognitive impairment [28]. This produces serious alterations in brain function, which can lead to necrosis and brain death if the situation persists over time [15].

### 1.1.1.2 Hemorrhagic stroke

Hemorrhagic stroke is produced by an extravasation of blood in the brain tissue and eventually extracerebral bleeding as a consequence of the rupture of a cerebral blood vessel. Of all strokes, hemorrhagic patients account for around 20% of cases [29]. However, its prognosis is much worse than in the case of ischemic strokes.

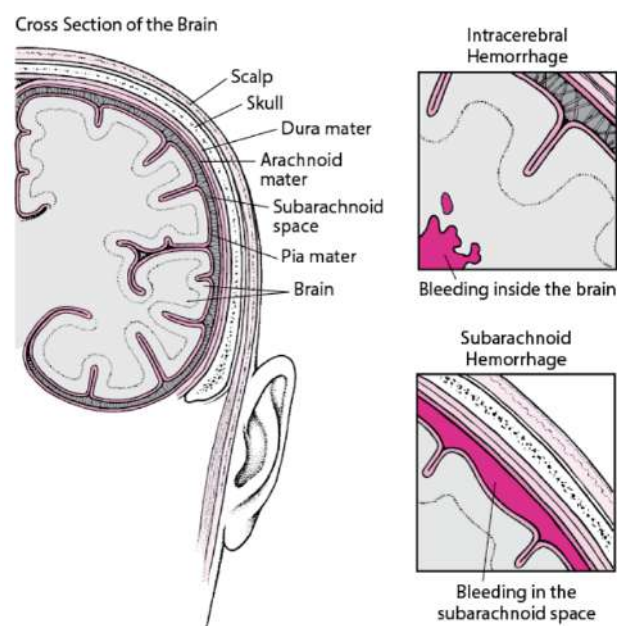


Figure 1.4: Diagram of the two main types of hemorrhagic stroke: intracerebral hemorrhage and subarachnoid hemorrhage [30].

Intracerebral hemorrhage (ICH) is the most common hemorrhagic stroke. It accounts for 10-15% of all stroke cases [31]. It consists of an accumulation of blood, or hematoma, within the cerebral parenchyma produced as a consequence of the rupture of a cerebral blood vessel. It can be classified as primary and secondary hemorrhage. The primary hemorrhage occurs in between 78% and 88% of cases [31], when the rupture occurs in the wall of a previously weakened vessel due to degenerative processes, such as amyloid angiopathy or derived from arterial hypertension. The secondary hemorrhage secondary occurs as a consequence of congenital malformations of the vessel, coagulation disorders, etc. [32].

Depending on the area in which the bleeding occurs, different types are distinguished: cerebellar hemorrhage, brain stem hemorrhage, hemispheric hemorrhage and intraventricular hemorrhage [17].

The hemorrhage causes an accumulation of blood within the brain parenchyma, which leads to an alteration of the normal anatomy of the brain and an increase in local pressure in the area [33]. According to the speed of expansion of the hematoma, the primary damage is distinguished during the following minutes and hours after the start of the bleeding, and the secondary damage as a consequence of the presence of intraparenchymal blood in the brain, which may depend on the volume of the hematoma [31].

Although inflammatory mediators in response to stroke produce an increase in brain damage, the role of inflammatory cells (such as microglia, macrophages, etc.) is substantiated for cleaning and removing cellular debris caused by the hematoma [34]. Following intracerebral hemorrhage, extravasated blood components and those associated with brain damage (blood-derived coagulation factors, complement components, immunoglobulins, and other bioactive molecules) produce a cytotoxic, prooxidative, and pro-inflammatory attack on adjacent healthy brain cells continuing tissue damage, which can be seen minutes after the start of bleeding [35–37]. 24 hours after the onset of ICH, the lysis of red blood cells begins, which produces the release of cytotoxic hemoglobin. The hemoglobin and its degradation products (heme and iron) are chemical substances with a high cytotoxic capacity, which alter the state of neighboring brain cells, causing cell death in many cases [34, 35, 38].

The most common cause of ICH is hypertension [39]. Hypertension can trigger hyperplasia in the small intracranial vessels, which favors their necrosis and rupture.

Clinically, it is usually presented in an acute form, with the presence of headaches, nausea, vomiting and a decrease in the level of consciousness, in addition to an increase in blood pressure. Among all those affected, the mortality rate ranges between 35% and 52% in the following 30 days [40], and only 38% survive the first year, suffering secondary injuries and serious neurological deficits as a consequence of the hematoma [31, 33].

### 1.1.1.3 Stroke risk factors

As explained before, ischemic strokes correspond to 80% of the total incidence of stroke in Spain today [3], and its etiology determines the most appropriate strategy for both treatment and secondary prevention [15]. While hypertension is the most common cause of ICH, there are numerous risk factors for ischemic stroke. The most notable ones are explained below:

- Age: Incidence almost doubled in each decade after age 55 [9].
- Gender: Women of childbearing age with hormonal disturbances [9].
- Genetic factors: Family history of stroke increases risk by 30% [9].
- Stress: Psychosocial stress is independently associated with an increased risk of stroke, more pronounced in women than in men [41].

- Obstructive sleep apnea: Increases the risk of stroke regardless of other risk factors such as hypertension [42].
- Arrhythmias: Atrial fibrillation that favors the formation of thrombi that can block cerebral vessels taking form of an embolus. It is the main risk factor for embolic strokes. Also other types of arrhythmia without atrial fibrillation increase the risk [43].
- Atheromatosis and arteriosclerosis: Especially carotid stenosis, where the degree of stenosis over 50% increases the risk of stroke that could be thrombotic or embolic through an arterio-arterial manner [44].
- Arterial hypertension: High arterial tension increases risk by 31% [43, 45].
- Diabetes mellitus and metabolic syndrome: diabetes increases the risk by 8%, type 2 diabetes increases the probability of suffering a stroke between 2 and 3 times [45, 46].
- Obesity and diet: The mechanisms that determine the increased risk are not clear. A diet rich in fruit and fish, as well as regular physical exercise play a protective role [45].
- Tobacco: The risk of stroke increases with the number of cigarettes smoked per day. Passive smokers have a 30% higher risk than unexposed people [47].
- Alcohol: More than 30 units per month is associated with an increased risk [48].
- Environmental pollution: Prolonged exposure increases the incidence of stroke between 4 and 19%, and short exposures but at high levels increases by around 3.5% [49].
- Hormonal and contraceptive treatments: Especially in menopausal women or over 40 years of age with obesity or smoking in addition to contraceptive treatment [50].

### 1.1.2 Stroke treatment

This section shows an outline of the main treatment routes for stroke, for which it will be important to distinguish between ischemic stroke and hemorrhagic stroke.

In ischemic stroke, treatment is based on restoring blood flow in the vessel that has been occluded. For this, the only pharmacological treatment currently approved are the intravenous tissue plasminogen activators (t-PA) [51], which should be administered within a **window of 4.5 and 9 hours** maximum after the onset of symptoms. This technique, called fibrinolysis, provides anticoagulant effects to dissolve the thrombus and restore blood flow. However, only about 15% of patients treated with this technique achieve a complete recovery [16, 52].

In cases of acute ischemic stroke due to large vessel occlusion, the treatment that provides the best results, and that can be combined with fibrinolysis, is mechanical or endovascular thrombectomy. This technique consists of the extraction of the thrombus through an endovascular catheter. However, mechanical thrombectomy can only be

applied within the first 24 hours, depending on the case, after the onset of stroke symptoms, and it can only be performed in certain specialized health centers, so many patients do not benefit from this treatment [16].

In addition to these two main treatments for acute ischemic stroke, in a second stage it is important to carry out a treatment to prevent new strokes. This usually consists of antiplatelet to prevent the formation of thrombi or anticoagulant drugs to prevent the formation of emboli, drugs to control blood pressure, and others to treat complications associated with the first stroke [53].

In hemorrhagic strokes the treatment is different. When possible, it consists of treating the injury by evacuating the extravasated blood through a surgical intervention [54], but in most of the cases is based on having the patient controlled (heart rate, blood pressure, glycemia, body temperature, fluid and electrolyte balance, hemostasis, intracranial pressure, etc.) and prevent and treat complications [55].

The speed of initiation of treatment is crucial for the recovery of patients. In a study carried out in Spain in 2006, the evaluation of the patient by a neurologist within the first 6 hours from the onset of symptoms was associated with a five times lower risk of poor evaluation [56]. On the other hand, [5] states that for every 30 minutes dedicated to reopening the artery, in cases of ischemic stroke, patient mortality increases by 20%. Therefore, early detection and speed of treatment is crucial for the evolution of these patients.

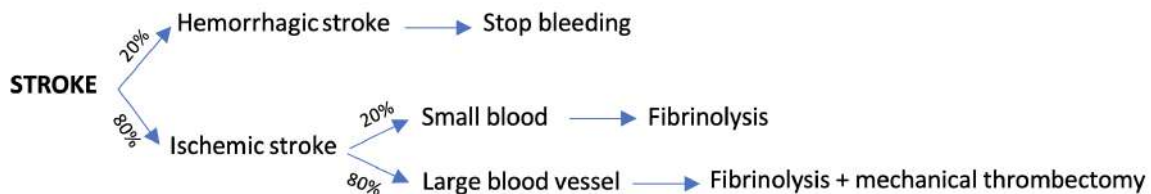


Figure 1.5: Diagram of types of stroke and their initial treatment when the patient arrives at the hospital.

### 1.1.3 Stroke aftermath: motor and cognitive sequelae

It is very common among stroke survivors to experience different types of sequelae and disabilities that affect them when they return to their daily lives, significantly reducing their quality of life after the disease. As seen in previous sections, stroke symptoms depend on the infarcted brain area, and the same occurs with sequelae. Focusing on the main interest of this thesis, here the sequelae are divided into two big groups: motor and cognitive sequelae.

#### 1.1.3.1 Motor sequelae: upper limbs

Motor sequelae refers to a partial or total impairment that leads to a loss of function of part of the body, usually the extremities. The most common motor sequelae of stroke are hemiplegia and hemiparesis, which implies that the side of the body contralateral to

the affected cerebral hemisphere becomes paralyzed or has markedly diminished motor strength. This is usually reflected as muscle weakness, lack of muscle control or even total paralysis. Motor dysfunction can occur in the upper limbs (UL), in the lower limbs (LL), or in both.

If during the acute phase of stroke, the patients experience some degree of UL motor deficit, it is likely that in the long term they will have difficulties to perform some ADLs [57]. Muscle weakness and sensory changes are the most common UL motor sequelae of stroke, which hinder the natural kinematics of the arm and hand, resulting in lasting functional limitation in approximately 70% of cases. These alterations often affect the hand's ability to shape correctly, alter muscle tone, and make it difficult to perform skillful and precise finger movements [58–60].

The functional consequences of UL impairment can be divided into three types: learned nonuse, learned bad-use, and forgetting [61].

- The term “**learned nonuse**” refers to the inability of the limb to perform functional activities due to lack of use after a stroke, generally as a consequence of weakness/paralysis or sensory loss caused by the stroke [61].
  - **Weakness** or **paralysis** is the predominant impairment after stroke [62, 63]. This occurs due to a lack of signal transmission from the motor cortex (where the impulse for movement is generated) to the spinal cord (which receives the signal and sends it to the muscles to execute the movement). This produces a delay in the onset and completion of muscle contraction [64] and therefore a slowness in muscle activity [65], even preventing movement.
  - **Sensory loss** in the UL can be tactile, proprioceptive, or higher order such as stereognosis and graphesthesia. These may be associated with the severity of the stroke and the degree of weakness [66], although sensory disturbances without motor weakness may also result from specific lesions in the parietal cortex [67]. Studies have suggested that sensory deficits may result in an inaccurate motor response, even though motor abilities were adequate to perform the task [68]. Therefore, it is believed that chronic loss of sensation may contribute to motor impairment, for example, due to the inability to adequately control motor activity due to the lack of sensory feedback [61].
- The term “**learned bad-use**” refers to the inability to move the affected limb correctly, due to weakness, sensory deficits and pain, as well as stiffness, spasticity and contractures resulting from temporary immobility, using instead what are known as “compensatory strategies” to carry out the tasks. These compensatory strategies involve making abnormal movements to accomplish the activity, such as forearm pronation and wrist flexion instead of neutral forearm position and wrist extension to guide the hand for grasping, and hand flexion. metacarpophalangeal joint rather than flexion of the proximal interphalangeal joint to grasp objects [69]. In this way, the patient can be able to carry out a task, but with little precision and poor performance, turning it into bad habits that will prevent optimal recovery. Spasticity and incoordination due to abnormal motor synergies can lead to the development of learned misuse [61].

- **Spasticity** is a motor disorder characterized by an exaggeration of speed-dependent reflexes with increased muscle tone and sometimes involuntary spasms, leading in most cases to a learned misuse of movements. The prevalence of spasticity increases with time since stroke [70] and is related to the secondary effects of weakness and immobility in skeletal muscles [71–73]. Initially, spasticity is considered a positive development, as it suggests that the nervous system is beginning to initiate repair mechanisms to restore muscle tone and movement. However, spasticity often evolves into stretch-sensitive forms such as spastic co-contraction [74], leading to involuntary movement in the opposite direction to the intended voluntary movement [61].
- The term “**forgetting**” refers to the inability to remember learned motor skills, as a consequence of interruptions in training and rehabilitation. Learning abilities, which would be stable in healthy individuals, are more transient after stroke. Therefore, 3 necessary processes have been established to achieve successful learning: test adaptation (and error detection), repetition, and reinforcement through rewards [61]. Several studies have shown that hand grasp and reach adaptation are impaired after stroke despite reasonable amounts of repetition of movements with the affected hand [69, 75–77]. This suggests that patients may be unable to effectively detect error with the affected hand [61], so supervised training appears to be necessary for this type of recovery.

### Scales for upper limb impairment evaluation

The most common tests used by therapists to evaluate different motor aspects of the UL and especially the motor function of the hand in stroke patients are described below:

- **Force:** the following scales allow measuring different muscle forces. They are used initially and at periodic retests to demonstrate an improvement in the force available for grasping or pinching [78].
  - Hand grip strength: evaluates grip strength by measuring the maximum isometric strength of the hand and forearm muscles. It can be done with various measuring instruments, from hydraulic dynamometers [79] to isokinetic dynamometers [80]. Is it usually done with an hydraulic or a digital hand dynamometer device [81].
  - Pinch force: allows to measure and evaluate the pinch force of the fingers individually. Is it usually done with an hydraulic pinch dynamometer [78].
- **Tone:** the following assessment allows measuring the muscle tone of the UL.
  - Modified Ashworth Scale (MAS): is used to assess the resistance experienced during passive range of motion. No instrument is needed to perform it. It is currently the most widely used method for the clinical assessment of spasticity and to assess the efficacy of pharmacological and rehabilitative interventions [82].

- **Manual dexterity:** the following scales allow measuring the ability to manipulate objects making coordinated hand and finger movements.
  - Nine Hole Peg test: it measures fine manual dexterity, which is the ability to manipulate objects using the distal part of the fingers. This involves precise, coordinated and rapid movement of the fingers when manipulating small objects [83, 84].
  - Box and block test (BBT): it measures gross manual dexterity, which involves global movements of the hand, less refined and precise, to grasp and manipulate larger objects [84, 85].
- **Functionality:** the following tests are widely used to assess functional capacity and movement control of the upper limb, especially in stroke.
  - Fugl-Meyer Upper Extremity Scale (FMUE): is used to quantify motor deterioration and recovery after a stroke. It assesses reflex activity, movement control, and muscle strength in the upper extremities [86].
  - Motricity Index (MI): is used to measure the degree of hemiplegia by examining the maximum isometric strength of the arm [87].
- **Sensitivity:** the following assessment allows measuring the sensory impairment on upper limb.
  - Nottingham Sensory Assessment (NSA): is used to identify sensory impairment after stroke and to monitor recovery over time. It measures tactile sensations over the skin, kinesthetic sensations (appreciation of movement, direction and position) and stereognosis (ability to recognize objects through touch) through different tests [88].

### 1.1.3.2 Cognitive sequelae

In addition to physical and motor disability, another very common consequence of a stroke is neuropsychological sequelae.

Around 80% of stroke patients have cognitive impairment in one or more cognitive domains, with attention, short-term memory, and executive function being among the most frequently affected cognitive abilities [89–91]. For example, in a study carried out in the Netherlands, 70% of stroke survivors would have information processing problems, and more than 40% would have memory difficulties, visuospatial and constructive deficiencies, and language disorders [92]. In addition to that, the sequelae of stroke often include depression, anxiety and other emotional disturbances as a consequence of the disabilities.

Focusing on the deterioration of cognitive functions, these, like physical sequelae, also have a negative impact on the quality of life of patients, affecting their ADLs [93]. Cognitive alterations involve different pathological processes and deficits in multiple domains such as attention, executive functions, memory, language, and visuoperceptive abilities. The prevalence of cognitive impairment resulting from a stroke probably varies according to the characteristics of the sample, the evaluation methods, the

definitions of impairment and the time interval from the onset of the stroke, therefore providing a prevalence figure is very complicated. Furthermore, under the cover of severe physical disability, post-stroke cognitive decline is likely to be ignored. The European Stroke Organization and the European Academy of Neurology, in their 2021 guidelines for the management of cognitive impairment after stroke, highlight the little attention paid to cognitive impairment caused by stroke, both in clinical practice and in research [94], while currently approximately 4 out of 10 hospitalized stroke patients have non-dementing cognitive decline in the first [95].

Due to the prevalence of cognitive impairment as a consequence of stroke, the term “vascular cognitive impairment” (VCI) has recently been introduced for any type of cognitive impairment, from mild cognitive impairment to dementia, caused by vascular pathology [96]. The signs or symptoms that occur during the course of the disease depend on the type, extent, and location of the underlying cerebrovascular pathology. Among all the possible cognitive alterations, the most disabling, which in turn hinders rehabilitation performance, is usually memory [97].

### Scales for cognitive impairment evaluation

Cognitive evaluation may change depending on the needs of patients and can be of great complexity. In order to simplify this, the most common tests used by psychologists to evaluate cognitive function are described below.

- **General cognitive function:** the most common tests for screening of cognitive impairment are:
  - Mini Mental State Exam (MMSE): it is a general test that detects serious cognitive problems with respect to “normal” cognitive function [98]. The MMSE has maximum score of 30, with five different domains of cognition analyzed: Orientation, contributing a maximum of 10 points, Memory, contributing a maximum of 6 points, Attention and calculation, as a measure of working memory, contributing a maximum of 5 points, Language, contributing a maximum of 8 points, and Design copying, contributing a maximum of 1 point. Individuals scoring higher than 24 are considered to be cognitively intact, although scores between 24 and 27 might be considered as mild cognitive impairment.
  - Montreal Cognitive Assessment Scale (MoCA): this is a more specific cognitive test that assesses the specific cognitive domains of memory, visuo-spatial ability, executive function, attention/concentration/working memory, language, and orientation [99]. Its maximum score is 30 and those patients scoring over 26 are considered to be cognitively intact. In comparison to MMSE, MoCA is considered to evaluate cortical and subcortical functions and to be more sensitive to detect mild cognitive impairments [100].
- **Specific cognitive domains:**
  - Stroop: is a color and word test used to assess the ability to inhibit cognitive interference that occurs when the processing of a specific stimulus feature

prevents the simultaneous processing of a second stimulus attribute (Stroop effect) [101]. It consists of 3 sheets, the first with the words "BLUE", "RED" and "GREEN" written in black repeatedly and in random order in different columns throughout the sheet, so that the patient must read aloud and the columns from top to bottom and from left to right as quickly as possible, saying aloud the color that is written. The second sheet has "XXX" written repeatedly across the entire sheet, but instead of being written in black, each set of "XXX" is written in red, blue, or green ink, in a random order, so that the patient to be evaluated says aloud the color of the ink of the crosses. On the last sheet, the words "RED", "BLUE" and "GREEN" appear again written all over the sheet, however, in this case instead of being written in black, they will be written with an ink of a color that does not correspond to the word, that is, the word "RED" will appear written in blue or green ink. In the latter case, the patient must inhibit his impulse to read the word that is written and say out loud the color of the ink of each word.

- Trial Making Test (TMT): is a test of motor speed and visual attention that consists of two parts. In Trail Making Part A (TMT-A), the subject must draw lines as fast as possible on a page where 25 numbers appear. In Trail Making Part B (TMT-B), the subject must draw the lines alternating between numbers and letters (numbers 1-12 alternate with letters A-L) [102].
- Digit Span Test: it is a test from the Wechsler Adult Intelligence Scale (WAIS) to evaluate attention and memory task, which consists of two parts [103]. The first one is the direct version, in which the subject must repeat a sequence of numbers in the same order that is presented, as a measure of the effectiveness of verbal attention [104]. In the second part, the inverse version, the subject must repeat the sequence in the reverse order of their presentation, which implies a mental scan involving verbal and visual processes, as well as working memory [105].
- Symbol Digit Modality Test (SDMT): this test from WAIS evaluates attention, visual tracking, mental processing speed and visuomotor speed. It consists of matching geometric drawings with a number from 1 to 9, according to a previous model. Different alternative forms described in some compendiums of neuropsychological tests have been developed [103, 106].
- Digit-Symbol Coding: this test, also from WAIS, measures processing speed, being sensitive to slow information processing, which may be affected by visual perception, short-term memory, and motor coordination [107]. It consists of copying abstract symbols associated with numbers as fast as possible in a set time interval [108].
- Corsi Blocks: is a visuospatial span test to evaluate spatial memory and visual working memory. It consists of a board with cubes randomly distributed. The test has two parts, the direct and the inverse version. In the first one, the subject must reproduce a sequence previously performed by the examiner in the same order; in the second, the subject must reverse the presented sequence [103].

## 1.2 Stroke rehabilitation

The amount and severity of stroke sequelae varies especially depending on the severity of the stroke and the speed of treatment, because the larger the affected brain area, the worse the prognosis for the patient's recovery. However, as these two aspects are in many cases uncontrollable and unavoidable, the improvement of most patients lies in the effectiveness of rehabilitation (RHB). Taking into account the trend in the increase in stroke cases and the disability that this generates in patients, in the coming decades it is estimated that the demand for rehabilitation and long-term care for stroke patients will increase 27% in the European Union [109].

Rehabilitation should begin early during the acute phase of the stroke, once the patient is clinically stable [110]. This first phase of rehabilitation is carried out while the patient is still admitted to the hospital. After this period, rehabilitation will be carried out on an outpatient and home basis, because even when patients leaving the hospital are considered to be in a stable condition, they still have a long way to go to regain lost capabilities. For this second phase of rehabilitation that takes place when the patient is already discharged, they often have to visit rehabilitation centers on a daily or weekly basis to keep training in order to improve functionality, and with so, approximately 50% of the them are likely to regain some functional use of their paretic UL [111, 112].

Regardless of the type of sequela, conventional stroke rehabilitation typically involves the following processes: (1) assessment, to identify and quantify the individual needs of the patient; (2) goal setting, to define realistic goals that the patient can achieved; (3) intervention, personalized training to try to achieve those goals; and (4) reevaluation, to review progress in relation to the established goals [113].

Due to the enormous variety of stroke sequelae, rehabilitation must be carried out by a multidisciplinary team to address each different aspect affected by stroke, for which physiotherapists, occupational therapists, speech therapists and neuropsychologists usually participate. However, stroke recovery strategies are often delivered separately in terms of motor and cognitive RHB [114]. Both approaches have typically been applied at different recovery times, doses, and by different neurorehabilitation professionals without considering the concomitant effects that they might have on other abilities and domains [115].

### 1.2.1 Motor rehabilitation

As shown in previous sections, stroke can cause weakness, paralysis, or difficulties with movement in one or more parts of the body, depending on the location and severity of the stroke. Motor rehabilitation is usually the most challenging part in the recovery process. It aims to improve motor function and help patients regain maximum independence in their mobility and ADLs [116].

After a complete evaluation by different health professionals (mainly physiotherapists, occupational therapists, and speech therapists), the severity of motor impairments is determined and personalized rehabilitation goals are established.

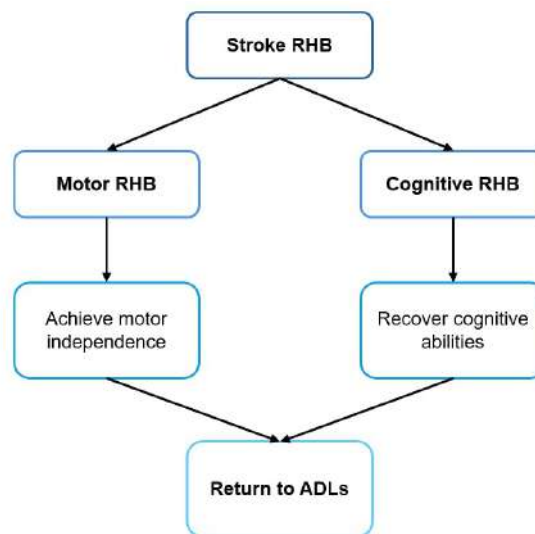


Figure 1.6: Two main types of rehabilitation after a stroke and the main objectives they aim to achieve.

Physical therapists work on improving muscle strength, coordination and balance through therapeutic exercises and mobilization techniques. It usually consists of the execution of repetitive movements, focused on regain function in affected limbs and learn unlearned physical activities if necessary. Occupational therapists focus on helping patients perform activities of daily living, such as dressing, bathing, cooking, and eating, independently or with as little assistance as possible. In some cases, assistive devices such as orthoses, wheelchairs, walkers, and robotic therapy systems are used to facilitate motor rehabilitation by both physical and occupational therapists (1.3.1 shows the most common rehabilitation technologies for upper limb motor recovery) [57]. Furthermore, speech and language therapists work on the recovery of communication and language, and are often included in this rehabilitation process since some stroke patients may experience speech and language difficulties due to involvement of brain areas related to language processing.

### 1.2.2 Cognitive rehabilitation

Cognitive therapy involves a variety of techniques and strategies designed to address affected cognitive areas, and it is frequently carried on by neuropsychologists and occupational therapists. Some examples of cognitive therapies and approaches commonly used are [117]:

- Memory training: Strategies are taught to improve memory, such as using reminders, organizing information, and practicing retrieval.
- Attention training: Exercises and activities designed to improve concentration and sustained attention are worked on.
- Language rehabilitation: If the patient has experienced language difficulties, speech and language recovery exercises are performed, as well as communication practice.

- Spatial perception exercises: For patients with spatial perception problems, exercises can be performed to improve spatial orientation and awareness of the environment.
- Executive functions exercises: Skills such as planning, decision making and reasoning are worked on.

### 1.2.3 Combined motor and cognitive rehabilitation

Currently, new lines of research are emerging that suggest overlapping effects between these interventions [118]. There is evidence that strength may be a predictor of cognitive function [119], and it has been proven that the practice of manual strength exercises has a beneficial effect on general cognition in healthy adults [120] and in mild cognitive impairment [121]. In addition, UL motor rehabilitation can improve global cognitive status, but also some specific cognitive domains such as attention and executive functions in other disorders such as Parkinson's disease [122]. However, there is a notable paucity of evidence about the effects of hand motor interventions on the cognitive status in stroke, in a recent literature review included in this thesis, motor interventions were found to improve MoCA/MMSE scores post-stroke, being the best interventions robot-assisted hand training and strength training. Nevertheless, the lack of high quality evidence evaluating cognitive variables in motor rehabilitation protocols was confirmed [123].

Therefore, post-stroke rehabilitation that considers both motor and cognitive aspects is essential to achieve optimal patient recovery and for them to have the best possible quality of life after the disease [124].

Over 20% of stroke survivors have concomitant motor and cognitive impairment in long term [125]. Recent investigations show a pathophysiological and structural correlation between cognitive and motor deficits in stroke survivors. Specifically, studies suggest that global cognition, memory and executive functions are closely linked to the motor performance of these patients [125]. This could be explained by the role of the frontal lobe in the provision of executive functions and motor control, as it appears to be the underlying basis for the coexistence and close interactions between cognition and fine motor skills [126]. The underlying neural connections that motor and cognitive functions share, holds the key to understanding why cognitive and physical performance declines occur simultaneously after stroke [127]. These changes may be due both to direct damage caused by the stroke and to changes in the structure and function of connected brain areas (diaschisis) that are located at a certain distance from the lesion, which affects broader areas of the neuronal network [128].

Figure 1.7 shows the information processing pathways for motor control, with the most important connections between the basal ganglia and the cortex, which involve motor and cognitive aspects.

Focusing on UL, several studies show the close relationship between the general cognitive state and the function of the UL motor function, pointing out that the cognitive demands directly influence the motor performance of the hand [129, 130]. Specifically, motor variables such as coordination and reaction times could be influenced by the

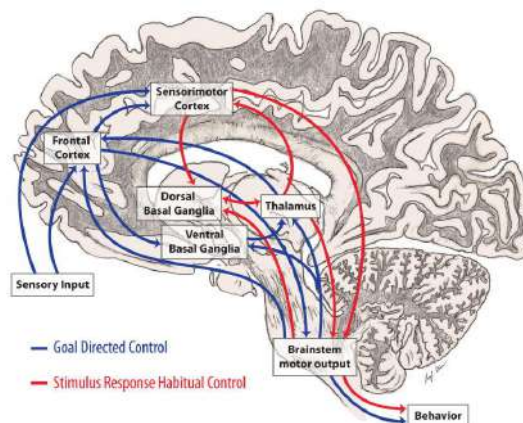


Figure 1.7: Cognitive and Motor Control [126].

cognitive state, affecting the performance of manual tasks [130, 131]. Other investigations show that there is an association between handgrip strength and an accelerated decline in global cognitive performance [132, 133], so that handgrip strength could be used as a potential early marker of cognitive decline [134].

In addition to this direct relationship, there are studies that indicate how cognitive impairment affects physical RHB, noting that the alterations in executive functions and attention resulting from stroke affect the progress of hand motor training [135, 136].

Furthermore, recent studies show concomitant effects in motor and cognitive stroke rehabilitation. For example, numerous comprehensive analyses have indicated that diverse forms of overall exercise training, including strength, aerobic, or ergometric exercises, can have notable positive impacts on cognitive function after a stroke [137–139]. However, it is crucial to note that this particular field of research has not received extensive investigation and does face some controversies [140, 141]. When it comes to rehabilitating the UL motor function, specialized training tailored to specific tasks and supported by robotic assistance has been proposed as a way to enhance the effects of neuropsychological rehabilitation on common deficits observed after a stroke, such as hemineglect [142, 143]. The favorable outcomes of this approach might be attributed to the functional reorganization of attentional networks, driven by the plasticity that occurs as a result of using and engaging the affected areas during rehabilitation [143].

While earlier preclinical [144] and clinical [145] studies have hinted at the possibility of simultaneous enhancements in cognitive function following hand motor rehabilitation in stroke patients, a comprehensive summary of the evidence has been lacking until now. Consequently, the primary goal of the systematic review carried out in Objective 1 during this investigation project was to analyze and combine the available data concerning the influence of hand motor rehabilitation on cognition after a stroke. Our objective was to ascertain the concurrent cognitive effects of motor interventions by aggregating results from randomized clinical trials that explored improvements in hand function variables through motor rehabilitation, with a particular focus on assessing cognitive variables as well.

### 1.3 Technologies for rehabilitation

The WHO (World Health Organization) recognizes as a therapeutic device any instrument, apparatus or machine used for the treatment or prevention of diseases [146]. New technologies are proving fundamental in the development of different clinical strategies, both for the detection of diseases and for the treatment and recovery of patients.

The concept “technologies for rehabilitation” encompasses the entire set of products and knowledge developed from rehabilitation engineering such as those used in the disciplines that study and treat disabilities. It is not only about tools or devices that contribute to carrying out RHB processes, but it also takes into account the functional capacity of people with disabilities and an easy design and handling for patients [147].

A frequent classification of technologies manufactured for rehabilitation distinguishes those commercial technologies from those tailor-made for the user. The former are manufactured in a standard way for any possible user, proving to be cheaper, such as wheelchairs, canes, etc. On the other hand, tailor-made technologies take into account the individual characteristics of the user through an initial evaluation, as is the case with different types of orthoses. However, it is true that the same tool can combine both types of devices, tailor-made and in a standard way, such as prostheses [147], which can present both advantages, turning out to be versatile for different types of users but also having an individualized component for each one.

The use of new technologies in RHB allows the use of traditional methods and tools in a way that increases their capacities and provides better results in rehabilitation processes. As an example, in the field of neuropsychology, the development of new technologies has made it possible to create computerized brain interface controlled prostheses and orthoses, evaluation programs by virtual reality and in real time, cognitive training programs, assistance tools, etc. [148]. Besides, new technologies can make rehabilitation more entertaining and dynamic by gamifying the trainings so that patients become more involved with the rehabilitation. In addition, they offer enough potential to create more comfortable and personalized rehabilitation and training systems for the patient, and also more detailed evaluation information that allows better patient follow-up, something especially interesting in neurological rehabilitation.

Within the entire range of medical devices, European Union (EU) 2017/745 legislation distinguishes four classes of devices based on the risk they pose to health. According to this regulation, the majority of diagnostic and rehabilitation devices belong to class IIa (moderate - low risk), since physiotherapy devices and also health software are included in this category. This regulation is important to take into account when developing new medical devices, since the European Union relies on it to grant the CE marking (which stands for “Conformité Européenne”, and means that the manufacturer of a product declares that the product meets all relevant European requirements for health, safety, performance, and environmental protection).

The following subsections detail different technological tools for upper limb motor rehabilitation and cognitive rehabilitation, explaining their main characteristics, the different existing types, their operation and showing some examples.

### 1.3.1 Technologies for upper limb motor rehabilitation

Within post-stroke physical rehabilitation, UL recovery takes on special importance as UL is essential to ensure independence in the performance of ADL, such as dressing, eating or drinking [149]. However, many patients get stuck in earlier phases of rehabilitation and are unable to regain fine control of the hands and fingers [150].

Currently, it is increasingly common to use different technologies to support UL therapeutic processes. On the one hand, there are video games and virtual reality systems [151] that stimulate the patient to perform different exercises in simulated environments. On the other hand, there are tools that support rehabilitation in a more direct way, such as robotic devices and sensor-based devices.

Robotic devices can be divided mainly into two types: active systems, which guide the execution of movement, and passive systems, which restrict the movement of certain joints [152]. Its use by the patient must generally be supervised by a specialized [150] therapist, and requires the patient to travel to specific rehabilitation centers that have this technology.

Sensor-based devices, instead of assisting in movements, sample and quantify the movement in order to know more precisely the condition and evolution of the patient, which is especially useful for home monitoring [153]. In this sense, wearable devices open up a multitude of possibilities in the field of home rehabilitation.

Focusing on UL and, specifically, hand rehabilitation devices (HRDs), an additional classification could be made dividing them into three categories: orthoses, exoskeletons, or end-effector devices [154].

All of these HRDs are new emerging devices designed to rehabilitate any motor aspect of the hand and to be used in any phase of rehabilitation therapy.

According to the recent Systematic Review carried out by Kabir et al [154], the following subsections show the currently available HRDs their individual description.

#### 1.3.1.1 Orthoses

Orthoses are devices that typically serve as support to protect the hand from postures and movements that can damage it. Some cover the entire hand and others cover each finger individually. Orthoses primarily provide support and alignment for rehabilitation. They offer strictly active rehabilitation therapy, with some devices providing additional components to allow for resistive training. They are typically low cost, light and easy to use, so the patient can use them from home. However, most of them don't have any actuators or sensors to perform resistive therapy and to be able to track any data and provide feedback on the performance. These braces' low profile inhibit them from competing with more developed exoskeleton devices. Examples of hand orthoses used for hand rehabilitation are: Saebo Stretch [155], Saebo Flex [156] and Script Orthosis [157].

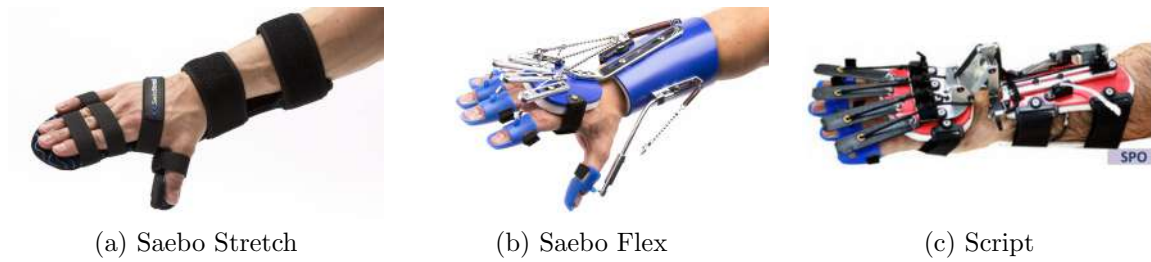


Figure 1.8: Examples of hand orthoses.

Table 1.1 explains the general description of each of the most used hand orthoses today.

Orthoses	Description
Script Orthosis [157]	It is an interactive hand and wrist orthosis that provides assistance for wrist and finger extension. It is compatible and adaptable, and interacts with motivating games based on ADLs.
Saebo Stretch [155]	It is a splint that offers support and flexibility for the hand. Promotes gentle stretching and extension of the fingers and wrist to reduce stiffness and prevent contractures while maintaining hand alignment. It is adjustable for different hand sizes.
Saebo Flex [156]	It is an orthosis that helps to extend the wrist and fingers. Through a spring system, it helps to open the user's hand to be able to release objects that were held.

Table 1.1: Hand orthoses and their description.

### 1.3.1.2 Exoskeletons

In contrast to orthoses, exoskeletons have additional components that provide powered functions to the user. Exoskeletons are motorized devices that improve the physical performance of the patient, acting on the individual joints of each finger of the hand, being able to adjust the design to each hand size. They have different sensors to provide a safety and controlled rehabilitation, and to provide a variety of exercises to be used in different phases of rehabilitation. With exoskeletons patients report greater recovery on their hand motor function than with orthoses. They are not heavy and are portable, so the patient can use them from home. However, its adjustment and adaptation to each hand is not easy, the control algorithms are complex, and their costs are usually much higher. Examples of hand exoskeletons used for hand rehabilitation are: ExoHand, HandMate and CyberGrasp.

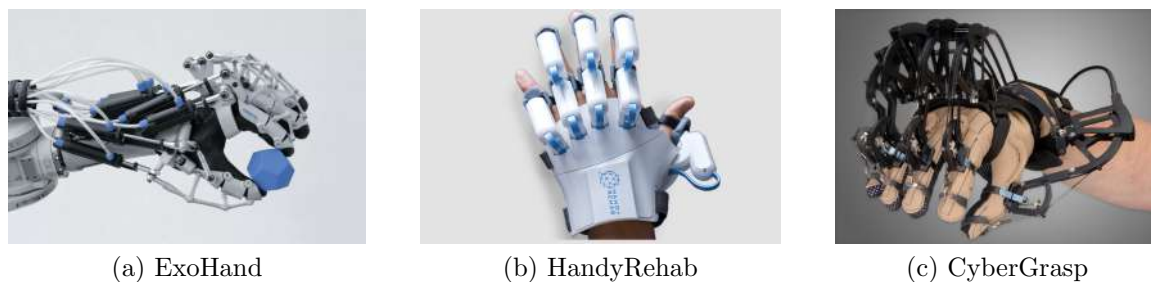


Figure 1.9: Examples of hand exoskeletons

Table 1.2 explains the general description of each of the most used hand exoskeletons today.

Exoskeletons	Description
HandMATE [158]	It is a portable, motorized hand exoskeleton in which each finger, including the thumb, is actuated by a linear actuator that provides flexion and extension assistance. Using FSRs, the device measures the grip initiation and extension force performed, and can act on selected joints in the hand.
Gloreha [159]	It is a pneumatically powered exoskeleton that actuates each finger via a cable-actuated system, working as a tendon during finger extension.
X-GLOVE [160]	It actuates each finger independently by actuating the joints of the hand through a linear actuation and link-based system. It allows free movement of each joint, including joint flexion and extension but avoiding hyperextension, and also portability and interaction with real objects.
PowerGrip [161]	It provides safe activation of the hand thanks to a linkage-based system and servo motors.
ExoHand [162]	It is a link-based exoskeleton that helps grasp and manipulate objects through actuators that achieve rotation of different joints. The system uses force and tension sensors, thus amplifying the force of the human hand, preventing fatigue and providing a controlled passive and active rehabilitation system.
CyberGrasp [163]	It is designed for rehabilitation in virtual reality environments. Through five actuators, a linkage-based system and FSRs (Force Sensitive Resistors), the device exerts individual grip forces for each finger and also provides resistive force feedback so that the user can feel the size and shape of simulated objects in the virtual world.

Exoskeletons	Description
Rutgers Master II [164]	It is a pneumatically actuated exoskeleton device with tele-rehabilitation and electromyography (EMG) sensors that can improve FMA scores.
PowerAssist Glove [165]	It is a soft robotic glove that uses flexible pneumatic actuators and pressure sensors in each finger, which provides assistance in hand function, allowing the rehabilitation of range of motion and grip strength.
REHAB Glove/Hagshenas-Jaryani [166]	It consists of five soft and rigid hybrid robotic fingers that, together with pressure and inertia sensors, apply a controlled flexion and extension movement to the fingers to provide rehabilitation.
SEM Glove[167]	It is a cable-actuated exoskeleton device that helps improve the user's gripping ability, through FSRs and linear actuators.
IronHand [168]	It is an assistance glove that, using FSRs, can serve as a training tool and help strengthen the hand.
Hand of Hope [169]	It is designed for EMG-driven robotic therapy that, thanks to EMG sensors, provides useful data for passive, active and assisted rehabilitation exercises performed with the device.
WearMe [170]	It is a wearable mechatronic glove that enables resistive motion tasks of the fingers and wrist, which includes inertial movement sensors to provide safe rehabilitation.
Exo Glove [171]	It is a soft portable robot that uses a linkage, FSR and EMG based system that allows for grasping objects and serves as a rehabilitation tool.
My-HERO [172]	Thanks to EMG signals and linear actuators, it controls and provides assistance in the extension of the fingers and grip strength.
Vanderbilt [173]	It uses motors and a linkage-based system to provide safe handheld actuation designed for patients with chronic hemiparesis of the upper extremities.
HandyRehab	It is a device based on EMG sensors with a variety of therapy programs designed for hand rehabilitation.
VAEDA [174]	It is a portable voice-activated exoskeleton device with motors, a cable-driven system, EMGs and tension sensors, designed for hand-focused therapy post-stroke.
ReHand [175]	It provides extension/flexion assistance for all five fingers of the hand using gear motors and a linkage-based system and that can be controlled via EMG signal and voice control.

<b>Exoskeletons</b>	<b>Description</b>
PneuGlove [176]	It is a device based on flexion force sensors that allows the rehabilitation of the hand in a virtual reality environment with a movement tracking system.
Tong et al. [177]	Using EMG sensors, it detects and recognizes the user's intention to move and helps the user perform hand movements in real time.
Wege's device [178]	It is a system actuated by cable and force sensors and EMG that allows to control the movement of the joints of the fingers and improve the strength of the patient providing a passive rehabilitation.
ExoK'ab [179]	It allows a complete range of movement for all the phalanges of the hand and is designed to control the position and force-position for active and passive rehabilitation routines through force sensors.
VSFH [180]	Using FSR and a cable-actuated system, it allows flexion and extension of the fingers to be actuated, assists in manual tasks and provides rehabilitation. Includes a hand orthosis to maintain the functional position.
Meeker et al. [181]	It is used for passive rehabilitation that uses EMG signals to perform movements that allow tasks of picking up and placing objects.
Flexohand [182]	It is used for passive rehabilitation of the hand and the only exoskeleton capable of independent action of each rotation of the fingers of the hand.
Delph et al. [183]	It uses a system of cables and servomotors to open and close the patient's hand, and tension and EMG sensors to assist or resist the user's movement. It can be controlled through a software program or by EMG signals.

Table 1.2: Hand exoskeleton devices and their description. Adapted from [154].

### 1.3.1.3 End-effector devices

End-effector devices differ from exoskeletons because they do not control the entire finger, the actuation over the joints is based on end point control. Typically, these devices are stationary, that is, it is necessary to fix the hand to use them. As exoskeletons, they have several sensors, so they can provide a high level of control and feedback, which also makes them more complex and expensive. In contrast to exoskeletons, end-effector devices incorporate higher sensing capabilities and games to engage the patients, and also much simpler control mechanisms without sacrificing overall rehabilitation progress. However, as they are stationary devices, they cannot be portable and

are limited to a singular location, which can be inconvenient. Examples of end-effector devices used for hand rehabilitation are shown in Figure 1.10.

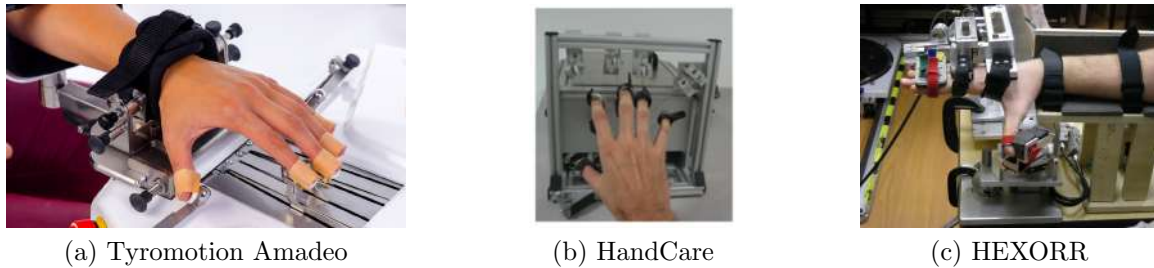


Figure 1.10: Examples of hand end-effectors

Table 1.3 explains the general description of each of the most popular hand end-effector devices.

End-Effectors	Description
Tyromotion Amadeo [184]	It is a sensor-based device that allows individual movements of the fingers, with evaluation and rehabilitation programs for strength, tone and spasticity. Some trainings are based on EMG signals.
HandCARE [185]	is a cable-actuated rehabilitation system that allows movement and control of the strength of each independent finger for opening and closing movements of the hand.
RehaDigit [186]	It is designed to repeat passive movements controlled by a vibration motor that acts on the different joints of the fingers.
Haptic Knob [187]	It is used to train the opening/closing of the hand and the manipulation of the knob through the use of force sensors.
Motus Hand [188]	It is designed to improve grip strength, spasticity, tone and coordination using kinematic and EMG sensors, with a user interface for home use.
HEXORR [189]	It provides hand rehabilitation to train gross grasp without individual finger control, using motors to assist finger flexion and extension and can lock motion to allow for isometric exercises.

Table 1.3: Hand end-effector devices and their description.

In addition to these devices included in the previous classification done by [154], we have found another very interesting and recently commercialized device that should be mentioned, Dextrain [190], which cannot be included in any of the above types. Dextrain is a medical device more similar to "end effector devices" but that does not control or act on any joint or part of the body. It is used externally as a tool for hand rehabilitation, holding on and performing different actions on the device, but not vice versa. It is designed for the diagnosis and treatment of hand disabilities

through visuomotor and audiomotor training exercises, with the main objective of improving dexterity. It allows individual training of the fingers, providing precise measurements of their execution, having training programs that can be customized according to individual needs and level of performance. Like the previous devices, it only focuses on recovering motor skills.



Figure 1.11: Dextrain Manipulandum [190].

Below, Table 1.4 shows the most important pros and cons of each type of HRDs, with particular emphasis on size and portability, cost, utility, and ease of use.

Device's Type	Use	Pros	Cons
Orthoses	Support of movements, assistive	Low cost; Light; Easy to use; Portable; Useful for first phases of RHB; Some interact with videogames	No control, feedback or tracking; Not for various stages of RHB; Not intended for cognitive RHB nor evaluation
Exoskeletons	For hand RHB and some also for assistance	Provides motor control and feedback; Light; Portable; Useful for various phases of RHB; Some interact with videogames	Expensive; Complex; Not intended for cognitive RHB nor evaluation
End-effector devices	For hand RHB	Provides motor control and feedback; Useful for various phases of RHB; Some interact with videogames	Expensive; Not portable; Not intended for cognitive RHB nor evaluation

Table 1.4: Use, advantages and disadvantages of the different HRDs.

### 1.3.2 Technologies for cognitive rehabilitation

After an exhaustive search to find a definition of the concept of cognitive rehabilitation, [191] finally framed it within the “set of techniques and procedures aimed at the enrichment, recovery or compensation of the cognitive abilities and functions of a subject whose level of cognitive functionality is limited or deficient”. This concept is generally applied in patients with brain damage, neurological deterioration or mental illness [192]. Cognitive training must be hierarchical and train one or more cognitive

skills, because when someone performs a task more than one cognitive domain is required [193]. In this way, within the technological tools for cognitive rehabilitation, we can find software programs focused on working on a single specific skill and others that follow more general strategies and objectives.

There is currently an increasingly entrenched trend to use **computer tools**, such as computers and smartphone devices, to use cognitive rehabilitation programs [194]. This type of tool offers a series of additional advantages over classic cognitive rehabilitation systems [195–199], such as:

- The ease of access to the tool, since the existence of home computers or video game consoles is nowadays very common in homes and in educational and rehabilitation centers.
- They facilitate the work of health professionals, since it allows a more efficient and comfortable management of the materials for the evaluation of the patient's evolution.
- They allow a quality and versatility in the presentation of materials greater than that of other traditional graphic and/or sound systems.
- The incorporation of additional elements, such as different sounds or images, increases the quality of cognitive stimulation and allows establishing multidimensional structures from a sensory perspective.
- They achieve a more motivating effect for the patient, resulting in less frustration.
- They allow the health professional to perform data analysis in a more efficient, powerful and reliable way. Work sequences and data analysis can be obtained automatically, saving time and effort on the part of the professionals.
- They allow the exercises to easily adjust parameters such as duration, level of difficulty, characteristics of the stimuli, etc., which enable personalized use adapted to the individual characteristics of the patient and their rate of progress.

It is important to be able to customize aspects such as the duration of each training session to allow the patient to progress without being distracted and exhausted. In addition, different stages or levels must be included in this rehabilitation tools that constitute a learning and evolution of the patient. However, it should not be forgotten that since it is a therapeutic process, this training must always be previously validated by a specialist clinician [200].

In [201], a systematic review was conducted to identify new cognitive stimulation, training and rehabilitation programs. The main advantages that they highlight are the ability that these tools provide to create specific treatments and personalized training, being optimized for portable and easy-to-use devices. Although, as in the case of the motor rehabilitation devices exposed in the previous section, many of these new tools are a bit ambiguous without being the individual objective of each one or the specific strategy they follow. Examples of this type of tools are CogniFit [202], CogniPlus [203], and NeuronUp [204].

### 1.3.3 Importance of gamification

Demotivation is very common among long-term rehabilitation patients, such as stroke. Traditional rehabilitation activities are often repetitive, demotivating and little stimulating for users in the medium and long term, even more for adult patients. In addition to that, motor rehabilitation is often painful, monotonous, and does not usually have a short-term visible results, so patients soon lose interest in their recovery process and home rehabilitation is frequently abandoned [150].

Recent studies show how game-based rehabilitation achieves greater positive effects on the user, especially regarding behavior and motivation, as in the case of video games [205]. In addition, video game therapy provides effective, lower-cost interventions that allow practicing activities of daily living with greater realism, motivation and dynamism, promoting active patient collaboration [206].

In order to motivate patients, [207] points out two basic foundations for the design of games for rehabilitation: the sense of the game and the challenge. The sense of the game refers to the relationship between the interaction of the user and the reaction of the system, which must consider the immediacy of the game's response and the evolution and adaptation to the user's progression. Regarding challenge, the video game must maintain the optimal challenge for the user, neither too easy nor too difficult, and gradually increase the difficulty as users improve their performances, so that it is not boring, but also does not demotivate the patient [207].

For this reason, after having introduced to stroke motor and cognitive sequelae rehabilitation pitfalls, as well as the various devices available for such rehabilitation with their own pros and cons, this project proposes a new paradigm in form of an innovative device. It combines cognitive and motor rehabilitation through interaction with a hand-operated, sensor-based modular and adjustable ergonomic device named AMBER (Portable and Modular device for comprehensive Brain Evaluation and Rehabilitation). The specifics of this device will be elucidated throughout this thesis, including hardware and software design features that enable its dual function. AMBER is designed for both cognitive and motor evaluation and rehabilitation of patients with upper limb motor impairments. The device focuses on the recovery and motor rehabilitation of the hand and fingers, enabling functional evaluation and the facilitation of training/rehabilitation sessions that can be conducted autonomously or under the guidance of a therapist. The use of the device is also intended to improve cognitive functions like perception, memory, and attention, with a particular emphasis on processing speed. It is important to say that this device serves as a supplementary intervention and does not replace conventional therapy. AMBER's design is compact and lightweight, enhancing its portability. Furthermore, its simplicity of use enables patients to use it within their natural environments, even at home, obviating the need for additional expensive hospital or rehabilitation center visits. Throughout this thesis, the significance of AMBER as a useful technological innovation with a clear socio-economic impact will be highlighted with a description of this design, validation and usability. We believe this device can really make a difference in cognitive and motor rehabilitation on patients suffering a stroke.

## 2. Objectives and Hypothesis

### 2.1 Objectives

#### 2.1.1 Main objective

The main objective of this thesis is to design, develop and validate a portable device capable of being used both for rehabilitation and for the physical and cognitive evaluation of patients, aimed to be used primarily for stroke patients.

#### 2.1.2 Secondary objectives

To this end, the following specific objectives are proposed to be achieved during the execution of the project:

- O1. Review and quantitatively synthesize the evidence regarding the impact of hand rehabilitation on cognition post-stroke.
- O2. Design a portable device capable of gathering data from the interaction with the patient's hand through sensors and colorful light stimuli.
- O3. Design a set of tests and tasks that can be carried out through the interaction with the device allowing the evaluation and training of hand motor variables and cognitive variables.
- O4. Validate the reliability of the device to extract motor and cognitive variables from the user.
- O5. Determine the usability of the device by therapists specialized in rehabilitation.

### 2.2 Working hypothesis

Our primary working hypothesis is as follows:

It is feasible to create a portable device that enables the evaluation and training of cognitive and hand motor variables, specifically for application in stroke patients.

In support of our primary hypothesis, we propose the following secondary hypotheses for this study:

- H1. There is evidence demonstrating a correlation between hand rehabilitation and cognitive improvement in post-stroke patients.
- H2. The designed device effectively captures data from user interaction.
- H3. Interaction with the designed device allows for the administration of a series of tests and tasks that facilitate the evaluation and enhancement of hand motor and cognitive variables.
- H4. The device exhibits a high reliability in extracting motor and cognitive variables from users.
- H5. Rehabilitation specialists perceive the device as user-friendly and advantageous for the rehabilitation of stroke patients.

## 2.3 Thesis organization

This thesis document is organized following the timeline of the tasks carried out during the development of this research to meet the objectives listed above. Each of the five objectives are explored in the chapters that follow. Chapter 3 addresses objective 1, Chapter 4 addresses objective 2, and so forth. Chapter 3 is reprinted from a manuscript that has been published and Chapter 4, 5 and 6 are an extension of a manuscript that is in second round of review for publication. The last chapters include the general discussion, limitations and conclusions obtained throughout the conduct of the entire research project.

# 3. Objective 1: Synthesize evidence on the impact of hand rehabilitation in post-stroke cognition

This chapter reflects the systematic review and Bayesian network meta-analysis conducted during this project on the effects of hand motor interventions on cognition after stroke, fulfilling Objective 1 (O1): review and quantitatively synthesize the evidence regarding the impact of hand rehabilitation on cognition post-stroke.

## 3.1 Methods

This systematic review followed the PRISMA 2020 statement [208] and was prospectively registered in PROSPERO (CRD42022377865). The reporting of the Bayesian Network Meta-Analysis (NMA) followed the PRISMA extension for this type of studies [209] and the ISPOR-AMCP-NPC guidelines [210].

### 3.1.1 Eligibility criteria

The selected studies must have had hand motor RHB intervention in a randomized controlled trial (RCT) targeting any of the following for people with hemiparesis post-stroke: hand function, hand strength, finger strength, hand dexterity and finger dexterity. In addition, the studies had to provide at least one outcome measure of a cognitive variable concomitant with hand motor variables but not providing formal cognitive interventions as part of the experimental protocol, it is, cognitive interventions delivered by a licensed neuropsychologist. There were no restrictions on the outcome measures, but only the following cognitive domains were considered for inclusion: global cognitive function, attention, memory, executive functioning, praxis and perception. Therefore, other cognitive domains such as decision-making, goal setting, social cognition or language were excluded. Articles were only selected if they were written in English and/or Spanish, and publication dates were the earliest available within each database.

As explained in our systematic review, we defined hand motor interventions as “therapeutic approaches aiming to produce an improvement of hand function through movement and/or practice of functional tasks”, which included physical and occupational therapy interventions. Control group interventions included all types of alternative

treatments, including usual care, placebo or no intervention, cognitive RHB, non-invasive brain stimulation and pharmacological interventions.

The population for this review was defined as adults (> 18 years) with functional dysfunction of the hand as a consequence of stroke, regardless of the type of stroke, location of injury, or stage of course. Participants with any other neurological disease and people with diagnosed dementia were excluded.

Electronic searches were conducted in 6 databases from inception to November 2022: PubMed, Web of Science, Scopus, Cochrane Library (CENTRAL), CINAHL and Embase. The searches were run between 1-30 November 2022.

The search strategy was undertaken considering the combination of the following concepts: (1) stroke, (2) hand motor interventions, (3) hand motor function variables, and cognitive domains including (4) global cognition, (5) attention, (6) memory, (7) executive functioning, (8) praxis and (9) perception. The first three concepts were always present in all electronic searches and were combined with each cognitive domain separately to increase sensitivity. Search strings varied slightly depending on the MeSH terms within each database. The detailed search strategy can be found in Appendix A.

### 3.1.2 Study selection process

Screening was based on the following hierarchy.

For titles and abstracts:

- Study design was not observational.
- Participants were adults with stroke receiving hand motor interventions.
- Outcome measures of hand function variables were provided.
- At least one cognitive outcome measure was provided.

For full texts:

- Study design was randomized controlled trial.
- Cognitive interventions were not administered as part of the experimental condition.
- Cognitive outcomes were reported pre- and post-intervention.
- The publication was peer-reviewed.

Duplicates were first removed using the “deduplicator” online tool [211]. The software ranked duplicates as “extremely likely”, “highly likely” and “likely” based on the amount of their shared information. This process was manually checked by M.M.V<sup>1</sup> to ensure the software did not remove any potential study. After duplicate removal, two authors (L.V.L<sup>2</sup> and M.M.V<sup>1</sup>) screened titles, abstracts and full texts independently. In case of disagreement, consensus was reached by discussion and if this was not possible a third independent author decided.

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<sup>1</sup>M.M.V significa Marcos Moreno Verdú

<sup>2</sup>L.V.L significa Laura Valenzuela López

### 3.1.3 Data collection and qualitative synthesis

A data extraction table was developed in Microsoft Excel to collect information from the studies that met the inclusion criteria. Data items included: (1) the number and characteristics of the participants, including age, gender, type of stroke (ischemic or hemorrhagic), lesion location (cortical or subcortical and blood vessel affected where available) and time after stroke onset (in weeks if possible), that defined the recovery phase (acute  $\leq 3$  months, subacute = 3-6 months, chronic  $\geq 6$  months), global cognitive function and global upper limb motor function, were collected and divided into the intervention and control group wherever possible; (2) the features of the interventions, including nature (conventional RHB or other interventions) and dosage (minutes per session, sessions per week, total number of sessions and total number of hours of therapy); (3) the outcome measures for hand motor variables and cognition (including global cognition, attention, memory, executive functioning, praxis and perception separately where available); (4) the main results of the trial, including pre-post within-group differences and between-group differences at post-intervention.

### 3.1.4 Quantitative synthesis: Bayesian Network Meta-Analysis

For continuous outcome measures with enough number of comparisons, a Bayesian NMA was applied. The statistical analyses were performed in R (version 4.1.3, R Core Team 2023) using the 'BUGSnet' [212] and 'gemtc' [213] packages. The Bayesian NMA was computed using the Markov Chain Monte Carlo simulation algorithm with Gibbs sampling. For each outcome measure, the mean difference was computed as effect size. In the studies in which the results were reported as 95% confidence intervals, data were transformed into standard deviation (SD) using appropriate formulas [214]. The effectiveness of the treatments was analyzed using the surface under the cumulative ranking curve (SUCRA) and inspection of the rankogram, where larger values reflect greater probability of effectiveness for each intervention. Direct comparisons between treatments were analyzed as mean difference (MD) with 95% credible intervals (CI) through a league table, and forest plots if statistically significant differences were found. In each NMA, the selection of a random or fixed effects model and presence of inconsistency were assessed [215]. In the case that a variable presented enough comparisons, the presence of inconsistency was also evaluated using the node-split method. In addition, if discrepancies were detected in the plot of posterior mean of consistency vs. inconsistency models, an additional meta regression model was applied adding as covariables age and baseline scores. The convergence of the posterior distributions of the parameters through Markov Chain Monte Carlo sampling was evaluated with the trace plot of mean of each comparison over all the iterations, as well as with the density plot of the subsequent effect size estimate. Further details on Bayesian NMA methods can be consulted in Supplementary Materials. Publication bias was assessed with D measure based on the Robust Bayesian Copas selection model defined as negligible ( $< 0.25$ ), moderate (0.25-0.5), high (0.5-0.75) and very high ( $> 0.75$ ) [216].

### 3.1.5 Risk of bias assessment

The Risk of Bias 2 (RoB 2) tool from the Cochrane Collaboration was used. RoB 2 is structured into a fixed set of domains of bias, focusing on trial design, conduct and reporting. Each assessment focuses on a specific result from a RCT. Within each domain, a series of questions aim to elicit information about features of the trial that are relevant to risk of bias. A judgement about the RoB arising from each domain is proposed by an algorithm and can be “Low” or “High” or express “Some concerns”. The overall RoB result is the least favorable assessment across the domains of bias.

## 3.2 Results

### 3.2.1 Selection process

The flow of information is shown in Figure 3.1. From 4540 records initially identified, 2269 were duplicated and 2164 were excluded after title screening. From the remaining 107 studies, 57 were excluded after abstract screening. Fifty full texts were sought for retrieval and 39 were assessed for eligibility, of which 15 were finally included in qualitative synthesis [217–231] and 11 in quantitative synthesis via NMA [217–227].

### 3.2.2 Study characteristics

All the included studies were RCTs with parallel design which implemented hand motor interventions in people with stroke and collected at least one cognitive outcome measure pre-post intervention.

### 3.2.3 Participant characteristics

A total of 714 participants (287 females, mean age = 62.35 years) were included. A table with the characteristics of the included studies according to participant features is shown in Appendix A. The average age was 61.60 years in the experimental groups and 63.11 years in the control groups. Regarding the stroke side, data from 349 of the 714 participants were retrieved. Among the reported data, 189 (54.15%) of the strokes were on the left side. In the case of the type of stroke, not all the data were reported either. Data from 365 participants were reported and 284 (77.8%) of the strokes were ischemic and 81 were haemorrhagic. The post-stroke time was heterogeneous, including patients in the acute, subacute and chronic phase, with the average time of the reported data of 234.69 days, which corresponds to chronic stroke. However, most participants were in the acute or subacute phase (446 of 648 participants from the data reported).

### 3.2.4 Intervention characteristics

Seven studies combined conventional RHB with virtual reality (VR) training, 5 studies with robot-assisted training and 3 studies with strength training as experimental interventions. A table with the characteristics of the included studies according to interventions’ features and outcome measures is shown in Appendix A. Conventional

RHB alone was the main control intervention (13 studies), either combining occupational therapy and physical therapy or in isolation. One study combined RHB with VR training as the control intervention. The amount of therapy received was matched between experimental and control groups. Intervention's dosage ranged between 30-120 minutes/day, 1-5 sessions/week and 2-12 weeks. The total amount of treatment received ranged between 450-2160 minutes.

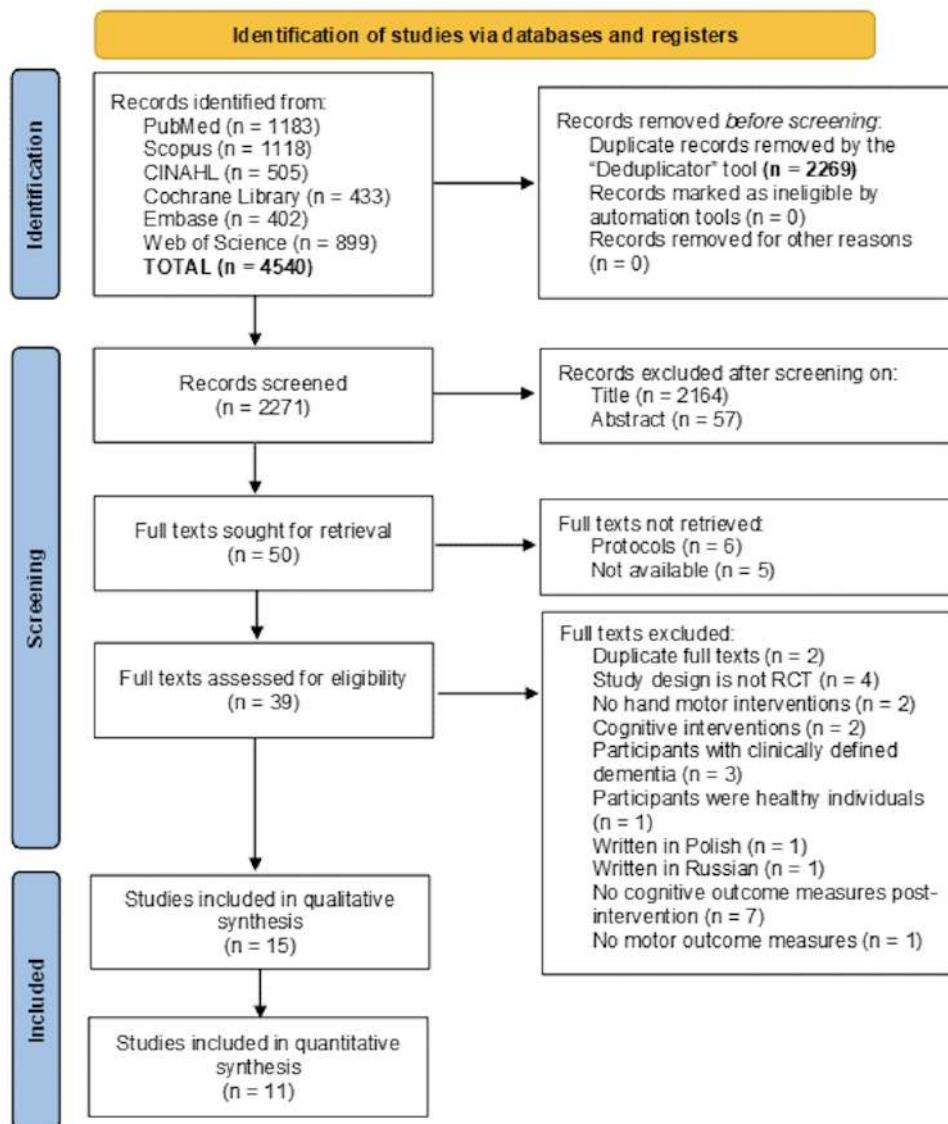


Figure 3.1: PRISMA 2020 flow diagram.

### 3.2.5 Outcome measures

Five studies utilized the Montreal Cognitive Assessment (MoCA) as the unique global cognitive measure, and 3 studies utilized the Mini-Mental State Examination (MMSE). Three studies provided data from both the MoCA and MMSE simultaneously. Three studies utilized the Addenbrooke’s Cognitive Assessment-Revised (ACE-R) as an overall score for global cognition, one of which also utilized the MoCA. Two of the studies utilizing the ACE-R overall score also provided data according to its specific cognitive domains (attention, memory, fluency, language and visuospatial). Six studies assessed different cognitive domains with specific outcome measures, including the Albert Test (n=1), the Trail Making Test (n=2), the Wisconsin Card Sorting Test (n=1), a Reaction Time paradigm (n=1), visual and auditory Computerized Performance Tests (n=1), and the Stroop Test (n=2). Therefore, attention, memory and executive functioning were the main cognitive domains assessed.

### 3.2.6 Risk of bias assessment

The majority of the included studies (n=10) were categorized as “some concerns” in overall risk of bias and the remaining (n=5) as “high”. In Domain 1, 7 studies had low risk of bias and 8 studies “some concerns”. In Domain 2, 10 studies had “some concerns” and 5 had high RoB. In Domain 3, all of the studies had low RoB. In Domain 4, only 1 study had “some concerns”, the remaining (n=14) had low RoB. In Domain 5, 10 studies had low RoB and 5 studies “some concerns”.

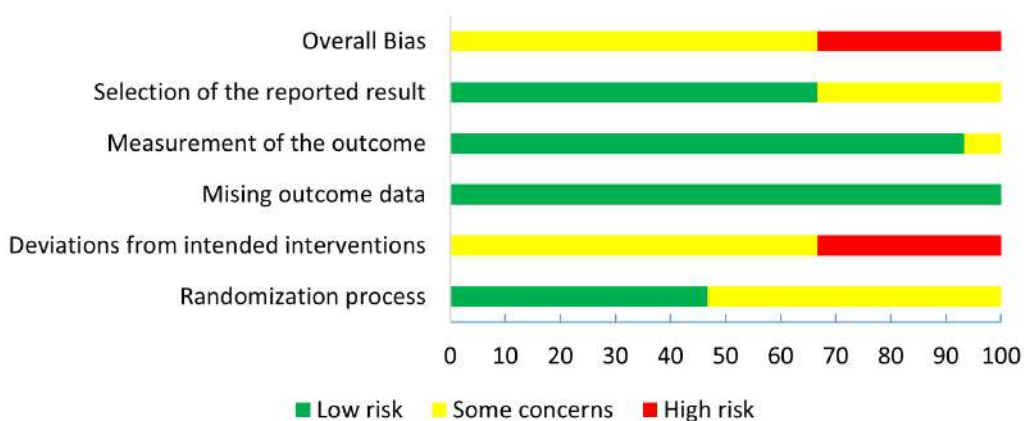


Figure 3.2: Risk of bias summary. Authors’ judgements broken down for each risk of bias criterion across all included studies.

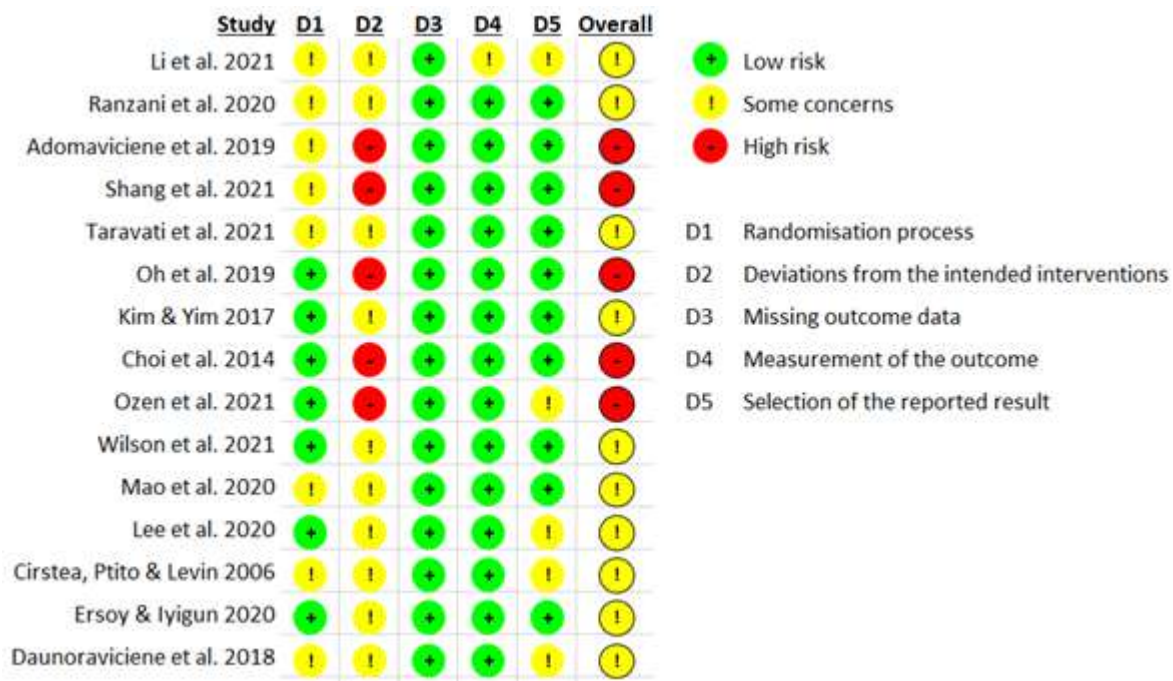


Figure 3.3: Traffic light risk of bias plot. Authors' judgements broken down for each risk of bias domain for every included study.

### 3.2.7 Effects of hand motor interventions on global cognition: qualitative synthesis

Most studies (n=8) found positive effects of conventional RHB on global cognition, whereas 4 studies did not find significant within-group differences between pre- and post-intervention. All studies that examined the effects of VR training found positive effects on global cognition. Three studies that examined the effects of robot-assisted training found positive effects on global cognition, whereas 2 did not. Finally, positive effects of strength training interventions on global cognition were found in all the studies which implemented this treatment (n=3).

### 3.2.8 Effects of hand motor interventions on specific cognitive domains: qualitative synthesis

One study did not find statistically significant effects of either robot-assisted training + conventional RHB or RHB alone on the Albert Test, without between-group differences. One study obtained positive effects of strength training + conventional RHB on the Trail Making Test-B (but not on TMT-A) and on the Stroop Test, although the group receiving conventional RHB alone only showed statistically significant effects on the Stroop Test. No between-group differences were found in either case. One study found positive effects of VR training + conventional RHB on the Trail Making Test. One study found positive effects of VR training + conventional RHB on the Wisconsin Card Sorting Test and Reaction Times, as well as conventional RHB alone.

### 3.2.9 Effects of hand motor interventions on global cognition: Bayesian NMA

#### 3.2.9.1 Description of networks

Eleven studies were included in the Bayesian NMA with effects of four possible interventions on global cognition through MoCA and/or MMSE assessed. Three studies provided effects on both scales. Most studies used conventional RHB as the control intervention (n=10). Three studies compared conventional RHB with conventional RHB + strength training, 4 studies with conventional RHB + robot-assisted training and 4 studies with conventional RHB + VR training. One study compared two robot-assisted training with VR training both interventions coupled with conventional RHB. Therefore, four interventions were compared in the NMA for the variables MoCA (n=8 studies, total number of patients in network = 480) and MMSE (n=6 studies, total number of patients in network = 350): conventional RHB, strength training, robot-assisted training and VR training. The average outcome at post-intervention was 23.94 points for MoCA and 25.43 for MMSE. The number of direct comparisons was largest for the MMSE.

#### 3.2.9.2 Selection of the final model and model assessment

The random-effects model better fitted for MoCA and the fixed-effects for MMSE, both without leverage outliers (Figure 11.2 in Appendix A). The consistency model had a better fit than the inconsistency model for both the MoCA and the MMSE (Figure 11.3 in Appendix A). When posterior mean deviance of consistency versus inconsistency models were plotted, it showed some discrepancies in the MMSE (Figure 11.4 in Appendix A). However, node-split showed no significant differences ( $p > 0.05$ ) between the direct and indirect comparisons, which reinforced the consistency between studies. Both the trace plot and the density plot indicated that the number of iterations was sufficient for an adequate convergence of the models (Figure 11.5 in Appendix A). Meta regression was applied for the MMSE but did not change the degree of discrepancies between the consistency versus inconsistency models and therefore the simpler model without co-variables was chosen (Figure 11.6 in Appendix A).

#### 3.2.9.3 Ranking of interventions

The interventions with the greatest impact on the MoCA were strength training (SUCRA = 70.42) followed by robot-assisted training (SUCRA = 60.08) (Table 11.11 in Appendix A). In the MMSE, robot-assisted training (SUCRA = 84.41) was followed by strength training (SUCRA = 81.86). According to the rankogram, the most probable best intervention for MoCA was strength training (41.68%), followed by conventional RHB (33.46%). For MMSE, the most probable best treatment was robot-assisted training (53.61%) followed by strength training (52.89%). Tables showing SUCRA scores for each intervention and outcome measure (MoCA and MMSE) and Network characteristics are shown in Table 11.11 in Appendix A.

No significant differences were found between any treatment comparisons for MoCA. For MMSE, there were significant differences between robot-assisted training and con-

ventional RHB [MD = -1.497 (-2.604, -0.396 95%CI)] as well as between robot-assisted training and VR training [MD = -2.16 (-3.164, -1.153 95%CI)], both in favor of robot-assisted interventions (Figure 7A-B). The same was found between strength training and conventional RHB [MD = -1.419 (-2.477, -0.383 95%CI)] and VR training [MD = -2.082 (-3.606, -0.537 95%CI)]. No significant differences were found between robot-assisted and strength training [MD = -0.07 (-1.6, 1.43 95%CI)] These data is also shown in more detail in Appendix A.

#### 3.2.9.4 Publication bias

Publication bias was considered negligible ( $D < 0.25$ ) assuming different between-study distributions for both the MoCA and MMSE meta-analyses (Table 11.13 in Appendix A).

### 3.3 Discussion

The present systematic review synthesized the available evidence on the effects of hand motor interventions on cognitive outcomes in individuals with stroke. Fifteen studies were included in the qualitative synthesis and 11 studies in the Bayesian NMA. The Bayesian NMA examined the effects of four possible interventions on global cognition through MoCA and/or MMSE assessments. The results showed that combining strength training or robot-assisted training with conventional RHB had the highest probability of being the most effective intervention for improving global cognition in individuals with stroke, followed by conventional RHB alone or its combination with VR training. However, controversial results were found depending on the outcome measure utilized, as the differences between the interventions were not statistically significant for the MoCA in any of the indirect comparisons, although statistically significant for the MMSE. This may be explained by the fact that although both tests have shown screening validity for post-stroke cognitive impairment [232], they assess global cognition in non-identical ways [233]. MoCA was developed as a brief tool to screen subjects who present with cognitive complaints and usually have normal MMSE scores, distributing cases across a broader score range with less ceiling effect and greater sensitivity [234, 235]. This may have impacted on the statistical analysis, as the MoCA network had greater inter-study variability with respect to cognitive status at post-intervention than the MMSE, thus reducing the probability of statistically significant differences to be found. This may explain why the NMA did not yield significant differences between interventions for the MoCA as it did for the MMSE. Overall, the Bayesian NMA was performed with a quite limited number of direct and indirect comparisons available (8 studies in MoCA and 6 studies in MMSE, 4 different interventions each). This is at the boundary for applying this type of statistical analysis, even though the statistical models applied fitted reasonably well with the data and model assessment did not show relevant inconsistencies. However, despite statistical modelling had reasonably well fit, heterogeneity across studies was found regarding participant or intervention characteristics (e.g., evolution phase or dosage), which may have impacted the results.

Aside from the above inconsistencies, strength and robot-assisted types of training

seemed to be the most effective interventions to enhance global cognition post-stroke. Positive effects of strength training are consistent with a large body of research showing that handgrip training and grip strength are tightly related to global cognition in healthy old adults [129]. Plausible biological mediators of these effects have been studied, for instance grip force patterns and grip force control may be a direct result of cognitive adaptations during task learning and reflect sensory-motor network changes [236]. In contrast, the relationship between robot-assisted training and cognition is less well understood. It may be hypothesized that robot-assisted training is a more comprehensive intervention which combines training of several motor domains, including strength, motor control and synergies and cross-modal sensory processing thanks to multimodal feedback, as well as indirect training of cognitive domains thanks to the practice of more complex tasks [237]. This would require greater cognitive demands which are trained parallelly with motor components, resulting in a multimodal integration and coordination between sensory-motor and fronto-parietal networks [238]. Conversely, conventional RHB or VR protocols may have lacked these features in the included studies, what may explain why they ranked lower in the NMA [239].

The qualitative synthesis revealed that most studies found specific cognitive effects of hand motor interventions aside from global cognition, although less studies have been conducted and larger heterogeneity of outcome measures was found. Conventional hand RHB by itself had positive effects on attention, executive control and information speed processing, what is consistent with a growing body of evidence showing cognitive effects of other RHB schemes such as gait training [240], resistance training [241] or general exercise protocols on these domains [242]. Moreover, although the combination of conventional RHB with strength training improved different attention components significantly more than RHB alone [227], this was only investigated in one study. Regarding the use of robot-assisted training, one study did not find additional effects on attention measures whereas another did find statistically significant effects on visuospatial abilities, fluency and memory domains but not on language or attention and orientation (all measured by the ACE-R). On summary, the cognitive outcomes seemed to be focused on the central executive network, although a lack of formal comprehensive cognitive evaluation did not allow to conclude if there are relevant effects outside of this network. Finally, the combination of conventional RHB with VR training improved attention and executive control, but these effects were not superior to conventional RHB alone [224]. Collectively, these findings reinforce the idea yielded by the NMA on the lack of additional effects of VR paradigms to enhance cognition after stroke, which contrasts with evidence from studies in people with traumatic brain injury [243]. Further research is needed to elucidate the controversial results published so far on the effects of VR training on post-stroke cognition.

Altogether, the results of this systematic review highlight the importance of considering the clinical effects than hand motor interventions may have beyond purely physical aspects. This is in accordance with complementary work demonstrating positive effects of cognitive RHB on motor domains in people with stroke [244], but also in other neurological conditions [245]. Therefore, the underlying idea of a cognitive-motor interdependency becomes particularly relevant. From a clinical perspective, our results are congruent with observational studies showing that cognitive and motor domains

interrelate in people with stroke [246]. Based on the present systematic review, it is crucial for future research studying the effects of motor interventions post-stroke to consider including at least one global cognitive measure in addition to motor outcomes, to advance our understanding of the inter-relationships between motor and cognitive recovery.

## 4. Objective 2: Design a portable device capable of gathering data from the interaction with the patient's hand through sensors and colorful light stimuli

This chapter explains the steps followed to meet objective O2 "design a portable device capable of gathering data from the interaction with the patient's hand through sensors and colorful light stimuli".

### 4.1 Methods

To achieve the objective 2 of this thesis, the first step is the design of the hardware (structure and electronic components) of the new device, taking into account its intended use and end user profile. After the design, the development of the prototype of the device will be carried out based on the established design. These two steps are explained in detail throughout this chapter.

#### 4.1.1 Design

The beginning of this thesis arose from the identified need of a tool that could be used at home by the patients of a brain damage unit needing to rehabilitate hand motor variables such as strength and dexterity, most of these patients had also cognitive impairments. This type of patient was very similar to other potential patients such as neurodegenerative disease patients that might have cognitive problems but also have motor problems in the hand caused by weakness. For this device to be complementary to conventional RHB, it should be able to be programmed and graded in difficulty but also should be able to evaluate the performance progression of the patient in order to integrate its results in the RHB programming by the therapists.

Taking into account the results of the systematic review presented in the previous chapter, that demonstrated evidence of the dual impact of hand RHB on cognitive and motor aspects, the design of the device was oriented for dual cognitive and motor RHB.

#### 4.1.1.1 Requirements of the device

From this initial idea and design, various conversations were held with stroke specialist, clinicians and engineers to gather ideas and develop the most optimal design. In addition, exhaustive bibliographic searches were carried out on the sequelae of stroke and the technological tools currently available for rehabilitation, to gather ideas and examine the limitations that existing tools might have. The device should allow motor and cognitive function to work concomitantly, while being portable, so that it can be used from the patient's home, with very limited supervision, and economically affordable for a larger number of patients.

Taking into account all these information, the following general requirements were established for the system design:

- The device must be adaptable and ergonomic, capable of fitting both the right and left hand and adapting to different hand sizes.
- As a portable device, it must be small, resistant to drops and large forces, lightweight, allowing easy use in various settings, including patients' homes, without the need for external continuous assistance or additional hardware.
- Regarding the materials and components, a very important aspect is that this device is affordable, ensuring that it is cost-effective to manufacture and, therefore, economically accessible to a wide range of users, although no specific cost and production studies were made, the objective was to be able to be produced at a cheaper cost compared with the available devices for hand rehabilitation.
- The device must be able to measure different metrics, including strength and reaction times, in order to assess and train cognitive and motor aspects such as strength, motor coordination, processing speed and memory.

According to these established requirements, the following specific Non-Functional Requirements (NFRs) were established to take into account when developing this device:

- **NFR 1 Usability:**
  - NFR 1-1 Ergonomics: the system will allow it to be used by both the right and left hands, and will allow the position of the fingers to be adjusted to be able to be used by hands and fingers of different sizes.
  - NFR 1-2 Portability: the device will be small in size and lightweight so that it can be portable.
  - NFR 1-3 Resistance: The device shall be resistant so that different forces can be applied to it and survive drops without damage.
  - NFR 1-4 Inexpensive: the device must be made up of simple and cheap electronic components, so that it is affordable and accessible to a greater number of people.
  - NFR 1-5 Ease of installation: to install and use this device, it will only be necessary to have the device and a computer, Tablet or Smartphone to connect to it.
  - NFR 1-6 Ease of use: the controlling website of the device will have an easy and user-friendly interface allowing independent use without supervision.
  - NFR 1-7 Ease of analysis: the system will allow the possibility of storing data so that the results and evolution of patients can be seen by specialists.

- **NFR 2 Efficiency:**
  - NFR 1-1 Quick response: the system must have a very quick response when pressing the FSRs.
  - NFR 1-2 Light color variability: there will be different color lights, varying depending on the exercise.
- **NFR 3 Data security:**
  - NFR 3-1 Data protection: this system stores different type of data anonymously through a private and unique user code.
  - NFR 3-2 Data access: the data will only be accessible by clinical specialists.

The specific metrics that the device is capable of measuring will be discussed in subsection 5.1.1.2.

## 4.1.2 Development

This section explains the development phases of the device proposed based on the requirements previously exposed.

### 4.1.2.1 First Prototype

Taking into account the non-functional requirements explained previously, a first design for the device was proposed mainly focused on usability requirements: ergonomics, portability, resistance and economy. This first prototype is shown in Figure 4.1.



Figure 4.1: Initial design of the structure of the device seen from different angles

The initial design presented is composed of four individual cylindrical modules 3D printed with PLA (polylactic acid) material, which can be nested side by side and allow complete rotation on them. It was designed for use with either the right or left hand. Each finger, excluding the thumb, has a dedicated module that can be rotated and adjusted to accommodate different hand sizes and finger lengths. Each of the fingers used with the device, it is index, middle, ring, and little finger, from now on will be named as digit 2, digit 3, digit 4 and digit 5, respectively.

This design was made taking into account deep consideration of the biomechanics of the hand. Each segment or module of the cylinder has been designed to adapt to the natural curvature and kinematics of the fingers, thus allowing fluid and natural movements. The possibility of rotating and adjusting these modules guarantees optimal adaptation to the size of the hand and the position of each finger, an essential feature to maximize therapeutic effectiveness and reduce the risk of undue effort or tension.

From an ergonomic perspective, the device prioritizes user comfort. The adaptability of the modules ensures that any discomfort or pressure on specific points of the hand is minimized. Furthermore, the use of PLA in 3D printing provides an ideal combination of durability and lightness, making the device resistant to prolonged use, but without being burdensome or uncomfortable for the patient.

The design has also taken into account the possible integration of electronic components. These components, once incorporated into the hollow cavity inside, will allow the monitoring and evaluation of the patient's progress, transforming the device not only into a rehabilitation tool, but also into a means to effectively evaluate the state and progress of the patient.

Furthermore, from an economic point of view, this design allows the device to be used with both the right and left hands, and the rotation of its modules allows it to be used by patients with larger and smaller hands, so that the same device can be used by different patients, reducing costs and maximizing its usefulness.

#### **4.1.2.2 Second Prototype**

Starting from the first prototype presented in the previous section, a new prototype was proposed taking into account not only the biomechanics or ergonomics for the end user, but also possible functionalities that will be of interest for this device to fulfill its rehabilitative functions and both cognitive and motor evaluation of stroke patients.

This second prototype can be divided into two different components: sensory cylinder and electronics.

##### **Sensory cylinder**

The design of this device is focused on a cylindrical casing working as a sensory tool. The initial design, shown in the Figure 4.1, underwent considerable modifications to better fit the established requirements: the size and the internal diameter were enlarged to make it more comfortable to grip and the electronic components to fit inside, stops were established to prevent the cylindrical modules from turning excessively, the design of the area where the electronic components would be placed was modified, and the adjustment mechanism between modules was changed.

This way, the final design of each module is depicted in Figure 4.2. It is 24mm high, so the module offers ample space to place your fingers. The outer diameter is 65mm to ensure compatibility with large hands and long fingers without overlapping the thumb when gripping. Its small hole has been enlarged to accommodate indicator lights, and the circular surface, previously raised with relief, is now lowered so that the force sensors can be positioned and protected from damage. The inner diameter of the cylinders is designed to accommodate the electronics and wiring effectively. With this size, the cylinders are also easily graspable by small hands. In addition, the cylinder modules are engineered with stops inside, allowing limited rotation to achieve an adjustable position without causing damage to the inner components of the device, and the regions that hook one module to another are designed to prevent them from separating easily.

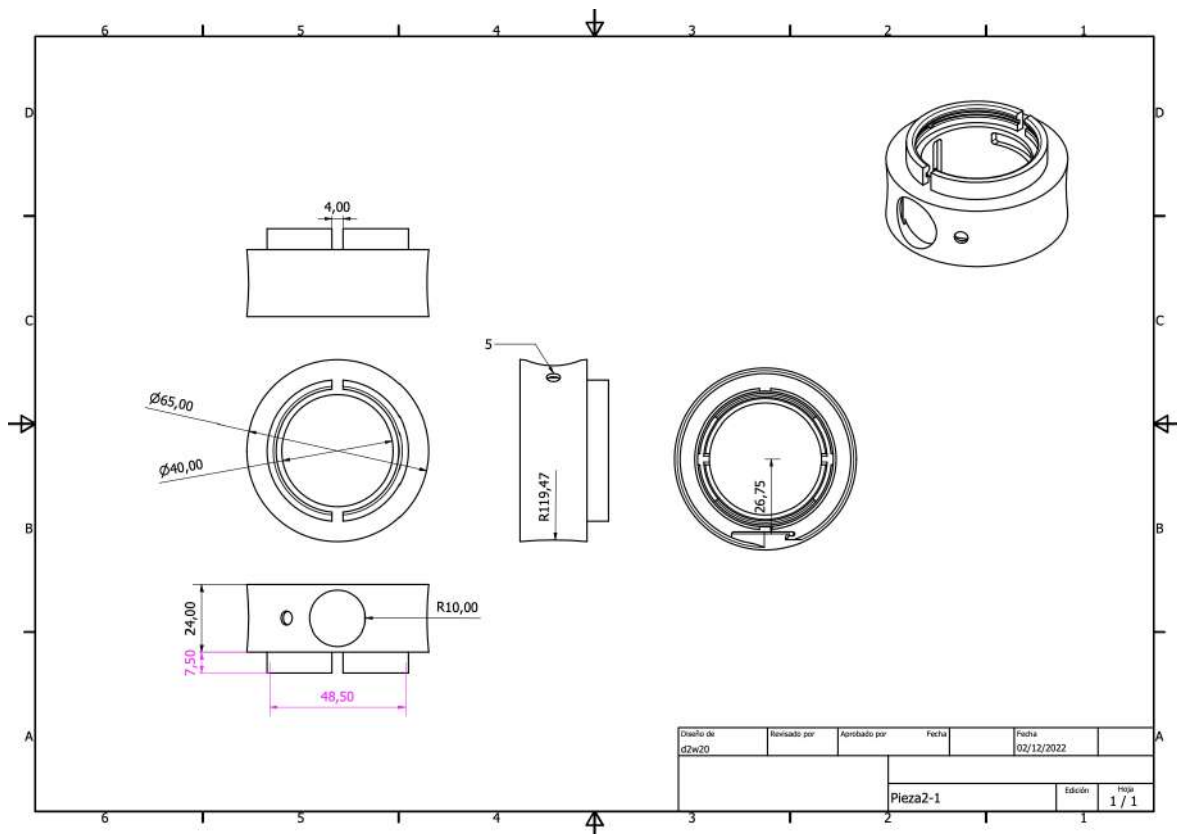


Figure 4.2: Sketch of the cylindrical modules of the device.

The structure, designed with a 3D modeling software (Autodesk® Inventor® 2022) as shown in Figure 4.3, is printed with PET (Polyethylene terephthalate) filament, a lightweight, durable and flexible material, a similar but better material than PLA in terms of durability, so that the structure of the modules is highly resistant to various stresses. This way, if a user squeezes it too hard, or if the device is dropped, the cylindrical casing won't break easily and electronic components will be protected.

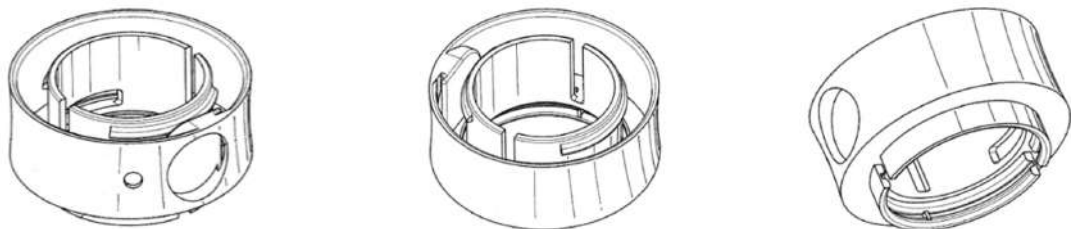


Figure 4.3: Sketch of a cylinder module of the device seen from different angles.

Each module features two holes: a small one for a LED, and a larger one with a flat surface below for the placement of a force sensor, which is positioned where the fingerprint will be placed. To grip the cylinder correctly, LEDs must always be visible and not covered by the fingers.

In addition to these four modules, as shown in Figure 4.4, two covers were designed and printed to be placed on both ends of the cylinder and hide all the components.



Figure 4.4: Final 3D design of the device.

### Electronic components

The electronics were also modified during the development of the device. Thanks to some fellow engineers from the CSIC (Consejo Superior de Investigaciones Científicas or Superior Council of Scientific Investigations in English), specifically from the Center for Automation and Robotics, changes to certain electronic components were proposed to improve the performance and functionality of the device. The replaced components were:

- Microprocessor Arduino Nano: this is a microprocessor with free and open source software that, despite being very versatile for a multitude of electronic projects, the functionalities and power it offered fell short for the needs of this project.
- LEDs RGB: are tiny LED bulbs used very frequently in electronic projects that can produce almost any color using the three primary colors (red, green and blue), however, there are other indicator lights such as Neopixel strips that were finally used in this project, which allow greater versatility, intensity adjustments, greater color clarity and ease of programming.

The final electronic system used for data processing and control in the device is battery powered and consists of the following components:

- a microprocessor Raspberry Pi Zero 2W.
- a battery power supply (PiSugar 3 Li-ion Battery).
- an analog-to-digital (ACD) converter (ADS1115).
- four Force Sensitive Resistor sensors (FSRs).
- four RGB LEDs (RGB Neopixel strip).

Figure 4.5 below shows the five main electronic components used to develop the device::

Subfigure (a) shows the microprocessor, a Raspberry Pi which serves as the core of the system to process all the data. This microprocessor model is the smallest in the Raspberry family (65mm x 30mm), so it fits inside the device. All other components must be connected to it to send and/or receive data. This microprocessor is equipped with an integrated Wi-Fi module, enabling a connection between the device and a

controlling website and an evaluation platform. It allows to be connected directly to an external power source, and also to connect a battery. Thanks to a microSD memory card that is connected to the microprocessor, functioning as if it were a computer's RAM memory, the operating system, the code for its operation, and the web server to connect to the website are incorporated into the microprocessor.

Subfigure (b) shows the battery. This is the ideal lithium battery for the microprocessor used, which has the same size to fit into the cylinder. It allows the device to have several hours of autonomy, but also allows it to be used connected, via a USB-C port input, to an external power source while charging if the battery runs out.

Subfigure (c) shows the analog-to-digital converter. This is used to acquired and transform the analog data from the force sensors into digital information that can be read and interpreted by the microprocessor. Its small size (18 mm x 28 mm) allows it to be housed inside the cylinder with the rest of the components.

Subfigure (d) shows a Force Sensitive Resistor sensor (FSR). The device has four FSRs, one for each cylinder module/finger, which are used to capture the force data of each of the fingers. A FSR is a polymer thick film device that exhibit a decrease in resistance with increasing force applied to the active surface. It is a very sensitive sensor which is optimized for use in human touch control of electronic devices. The sensitive area of the sensor is circular in shape with a diameter of 10mm, perfect for the size of fingerprints.

Subfigures (e) shows a RGB Neopixel strip. The device has four LEDs, one four each cylinder module/finger, to emit colorful lights through this stripe. The LEDs on the stripe allow for dynamic color changes and light intensities, so that it allows a lot of versatility for the operation of the device. The lights are used as an indicator for the operation of the exercises, and also to give visual feedback of the performance.

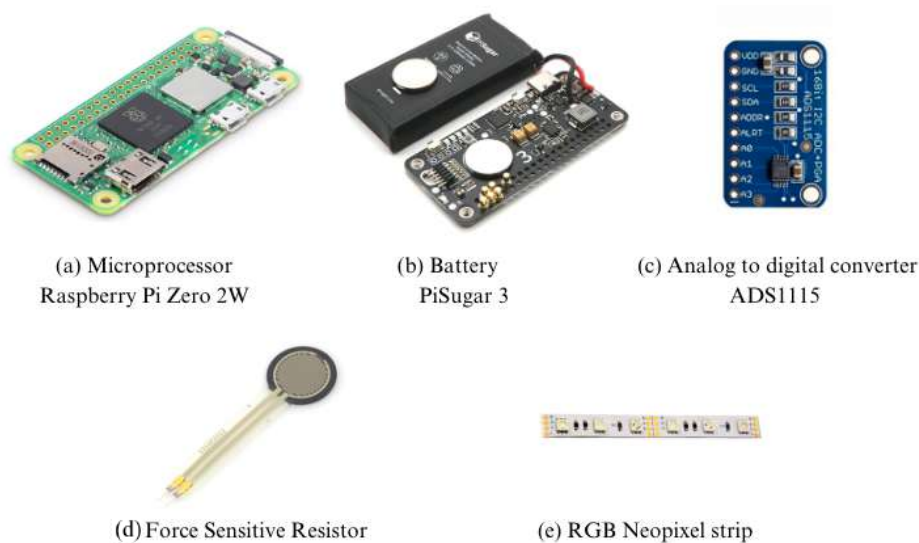


Figure 4.5: Electronic components of the device.

## 4.2 Results

The complete prototype of the device, made up by a 3D printer in PET material, is small in size, with a height of 17.5 cm and a maximum width (diameter) of 6 cm, and is lightweight, weighing 252 grams, which ensures its portability and ease of use. Inside the cylindrical casing, the following electronic components are housed: 4 Neopixel LEDs, 4 Force Sensitive Resistor sensors (FSRs), an analog digital converter (ADS1115), a Raspberry Pi Zero 2W microprocessor and a PiSugar battery, in addition to a button, placed in one of the covers, to turn the device on and off, and an additional LED next to it that will light up indicating that the device is on, all the components interconnected through small cables. Furthermore, a hole was made in one of the covers of the device at the height of the microprocessor's charging input position (USB-C type input), so that it can be plugged in to charge the battery. These electronic components can ensure the expected functioning of the device, allowing the programming and incorporation of different tasks for the evaluation and RHB of the hand motor and cognitive functions.

Figures 4.6 and 4.7 show the final prototype developed in this thesis. Figures 4.8 and 4.9 show the components housed within the final prototype and the additional button and hole to turn the device on/off and charge.



Figure 4.6: Final prototype of the device.



Figure 4.7: Rotation and grasping of the device.

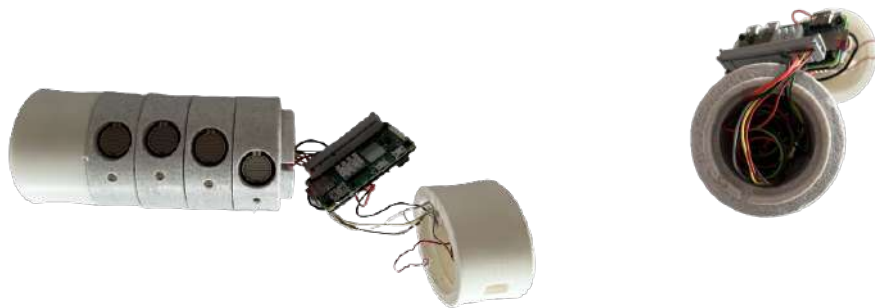


Figure 4.8: Electronic components housed inside the device.



Figure 4.9: Button and hole for the USB-C charging connection.

### 4.3 Discussion

The main purpose of this section was to meet the objective O2 "design a portable device capable of gathering data from the interaction with the patient's hand through sensors and colorful light stimuli". The design of the device described in this chapter required the consideration of important aspects of biomechanics, electronics and ergonomics adapted to a tool for rehabilitation and evaluation of the motor and cognitive abilities of the hand. This section presents the rationale behind the selection of certain materials and components over others.

Beginning with the design, the concept of individual cylindrical modules arose directly from the biomechanics of the hand. By mimicking the natural curvature and kinematics of the fingers, the device ensures that users can maintain natural and fluid movements during interaction. This feature stands in contrast to generic, one-size-fits-all designs which may not account for the varied sizes and morphologies of different hands. In this way, the design of our device is significantly different from others mentioned in the Objective 1, such as the Saebo Stretch orthosis, the ExoHand exoskeleton or the Amadeo end-effector device which, despite their effectiveness, present limitations in terms of shape and disposition of their grips. These devices, although they offer individualized grips for each finger, usually have flat surfaces or fixed structures that do not allow a complete and natural cylindrical grip. In contrast, our device offers a more intuitive and ergonomic grip experience, simulating the shape and natural movement of the fingers when holding cylindrical objects, as happens in many situations in everyday life such as holding a hairbrush, toothbrush, or a bottle of water. This feature is unique to our design and allows for a greater range of motion and exercises, which is essential for effective and personalized rehabilitation. Furthermore, the adjustment and rotation of the cylindrical modules in our device not only accommodate different hand sizes and morphologies, but also allow precise adaptation to the specific needs of each user, thus maximizing therapeutic effectiveness and comfort during use. From an economic perspective, the two-handed design (valid for left and right hands), adaptable to different hand sizes, emphasizes the scalability and usefulness of the device in various patient demographics. This adaptability ensures that the device is an economical solution for both rehabilitation centers and individual users.

Material selection also played a pivotal role in ensuring the device's robustness and usability. While PLA offered a balance between lightness and durability, the transition to PET filament in later designs optimized the device's resistance to external stresses. PET's inherent properties provide enhanced durability, thereby increasing the longevity of the device and protecting the inner electronic components from potential damages. In the field of hand rehabilitation devices, a variety of materials have been explored. For example, metal is valued for its strength and durability, but its weight and rigidity can limit comfort and portability. Rubber and silicone, on the other hand, offer flexibility and a comfortable grip, but tend not to be as durable in the long term and often lack the rigidity needed to protect sophisticated electronic components.

On the electronics side, the transition from the Arduino Nano to the Raspberry Pi Zero 2W was a key decision driven by the increasing computational demands of the device.

Although the Arduino Nano was an early choice due to its simplicity and reduced cost, its limitations in terms of processing power and lack of built-in connectivity proved to be significant obstacles to advanced development of the device. The Raspberry Pi Zero 2W, on the other hand, with its integrated Wi-Fi module, not only offers greater connectivity and data processing capabilities, but also facilitates real-time feedback and data logging, crucial aspects for tracking progress of the patient. There are other processors of similar size, such as the BeagleBone or the ESP32, that could have been considered. The BeagleBone, for example, offers powerful input and output capabilities, but its larger size and power consumption make it less ideal for a portable device. The ESP32, mostly used for its Bluetooth and Wi-Fi connectivity, could also be a viable option, but its processing power is inferior to that of the Raspberry Pi Zero 2W. The choice of the Raspberry Pi Zero 2W is thus justified by its optimal balance between size, processing capacity, connectivity and energy efficiency, critical elements for our device. Additionally, replacing traditional RGB LEDs with Neopixel RGB strips was a significant improvement. Classic RGB LEDs, although functional, had limitations in the variety of colors and light intensity. In contrast, Neopixel strips offer a wider range of vivid colors and allow for dynamic changes in color and light intensity, increasing versatility for device operation. Furthermore, programming Neopixels turned out to be simpler and more practical compared to traditional RGB LEDs. This, along with their flexibility and ability to provide dynamic feedback, makes them ideal for guiding patients through exercises and providing visual feedback on workout performance. Finally, the incorporation of Force Sensitive Resistor sensors (FSRs) serves as an optimal choice for capturing real-time force data from fingers. Their sensitivity and form factor, tailor-made for fingerprints, provides accurate and granular data essential for evaluating and monitoring patients' motor functions.

Among the possible limitations of the device design, there are some factors that impact its functionality and user adaptability. A notable limitation is the absence of a dedicated place and sensor to accommodate and measure the movements of the thumb. Given the thumb's pivotal role in hand function, this omission may restrict the device's ability to comprehensively evaluate and rehabilitate the full range of hand movements. Additionally, while the use of PET filament enhances durability, it may not provide the same level of tactile feedback as more flexible materials like silicone, potentially affecting user comfort during prolonged use. Lastly, the reliance on the Raspberry Pi Zero 2W, despite its advantages in processing power and connectivity, also introduces constraints in terms of energy consumption and heat dissipation, which could limit the device's operational time and durability.

In summary, this device's design and development embraces a multidisciplinary approach aimed at creating a versatile, efficient, and user-centered solution for hand rehabilitation and evaluation. Every design choice, from material selection to electronic components, converges towards meeting the objective of a portable, adaptable, affordable, and effective device, paving the way for future innovations in the field of medical rehabilitation devices.

## 5. Objective 3: Design a set of tests and tasks that can be carried out through the interaction with the device allowing the evaluation and training of hand motor variables and cognitive variables

This chapter explains the steps followed to meet objective 3. Specifically, it is focused in the software to complement the hardware presented in the previous point and explains the functioning of the device, the programming used, the controlling and storage website and its user interface.

### 5.1 Methods

To achieve the Objective 3 of this thesis, the first step is the design of the software, which means, the design of the functioning and programming of operation of the device. After the design, the development of the programming will be carried out based on the established design, to create the different exercises and modes of functioning. These two steps are explained in detail throughout this chapter.

#### 5.1.1 Design

In addition to the tasks/exercises mentioned to meet Objective 3, a website/application is also proposed to control the device and capture, store and display the data resulting from the assessments.

As for the tasks to include, on the motor side, grasping was the obvious task allowing functional use of the hand. Strength training was possible to perform with each finger individually and with the entire hand. Besides, interaction with sensors for cognitive exercises requires motor control, since interaction with a specific sensor requires good inhibition of the rest of the fingers. Finally, in tasks where rapid changes in finger interaction are required, motor control and coordination are challenged.

Regarding cognitive tasks, considering that our main target was the interaction of the hand, an area that is widely represented in the frontal lobe, executive tasks such as those implying reaction times and short-term memory were our goal. While these functions may seem distinct, they are all interconnected. For example, the speed at which we process information (processing speed) can affect how quickly we react to stimuli (reaction time), which in turn can influence on short term information recovery (memory). Similarly, the strength of hand grasp can be influenced by our reaction time and processing speed, particularly in situations that require quick, precise movements.

Therefore, rehabilitation of these functions involves a global approach that targets the entire frontal-parietal network. From the literature review presented in Objective 1, it is evident that motor enhancement or rehabilitation has a clear influence in cognitive performance. A possible reason for this is that by training and strengthening connections on this network, there are secondary benefits in other nodes connected to it. Details on the cognitive paradigms used to evaluate and train can be found in the description of the next chapter, which is dedicated to the validation of the system. Once completed the design of the device and the conceptualization of its functioning, it was evaluated and considered patentable. A European patent was requested, information regarding this can be found in Chapter 11 and Appendix C.

The following subsections explain how the device's tasks were designed. To do so, a first focus group was held with 8 stroke specialists from Hospital Beata María Ana (Madrid), including neurologists, neuropsychologists, physiotherapists and occupational therapists. After an explanation of the project's and device's objectives, different tests commonly used in clinical practice were proposed and analyzed to serve as a basis for designing the device's operation.

#### 5.1.1.1 Relationship between Device Tasks and Conventional Neuropsychological and Physical Tests

To design the specific tasks to be performed through the device, we studied the performance of different conventional physical and neuropsychological tests commonly used in the clinic for stroke evaluation and training. Based on these tests, the design of the device tasks will be carried out.

##### **Task 1: Strength**

The strength task of the device will be based on the user pressing the FSRs of the fingers, thus measuring the grasping and gripping capacity.

##### • **Related Conventional Tests:**

- Pinch Force: Evaluates the force between the thumb and the other fingers.
- Hand Dynamometry: Measures the maximum grip strength of the hand.

- **Evaluated Variables:** Both tests (pinch force and hand dynamometry), as well as the device task, assess grip strength and muscle tone. These variables are crucial in determining manual functionality, coordination, and recovery potential after neuromuscular injuries. They are widely used since their reliability has been proven in test-retest studies and others that relate it to the independence in ADLs following a stroke [247, 248].

- **Adaptation:** Of the two tests mentioned, the pinch force is the most similar to the operation of our device. However, the conventional way of performing this test (pincer grip between the thumb and the study finger) is further away from the way the device is gripped. For this reason, in this project the pinch force test was adapted so that the position of the hand in the grip was as similar as possible to the grip with the device. Hand dynamometry test was performed primarily to evaluate the relationship between hand grip strength and fingers strength with the device.

### Task 2: Reaction Times

The on-device reaction time task will assess how quickly a user responds to visual stimuli, thus measuring their processing speed and motor reaction.

- **Related Conventional Tests:**

- Stroop Test: Measures reaction time when naming colors, offering insight into attention and processing speed.
- TMT-A (Trail Making Test Part A): Assesses visual processing speed and hand-eye coordination when connecting numbers in a sequence.
- Finger Tapping and Detection tasks from Presentation® software: measure motor function and speed and information processing speed

- **Evaluated Variables:** The tests above along with the device task, assess processing speed, sustained attention, hand-eye coordination, and motor responsiveness. These variables are essential in determining an individual's cognitive and motor capacity, as well as their ability to perform daily tasks that require quick responses.

- **Adaptation:** The aforementioned tests are widely used to evaluate the cognitive level measuring processing speed in stroke patients [249–251], but their relationship with motor tasks and how they can discriminate between different degrees of functional disability is also studied [252]. For this reason, the device's tasks adapt conventional tests by integrating motor components of the hand.

### Task 3: Memory

The memory task on the device will require the user to memorize and repeat a sequence of lights, testing their short-term memory and working memory.

- **Related Conventional Tests:**

- Digit Span Test and Corsi Blocks: Both tests assess working memory by requiring patients to repeat sequences in the same order or in reverse order.
- Symbol Digit Modality Test and Digit-Symbol Coding: These tests measure working memory and processing speed when matching symbols and numbers.

- **Evaluated Variables:** Both conventional tests and the device task assess short-term memory, working memory, and the ability to retain and reproduce information. These variables are fundamental in determining the cognitive capacity of an individual, especially in scenarios that require the rapid retention and retrieval of information.

- **Adaptation:** Although memory dysfunction is not usually specifically studied in post-stroke patients, the aforementioned tests are usually widely used to evaluate memory [253]. For this reason, these tests have been adapted to the operation of the device, since it has been seen that this could help in the early detection of dementia and improve the quality of life of patients.

In summary, the tasks which will be implemented in the device present similarities and direct connections with conventional neuropsychological and physical tests, which reinforces their validity and usefulness in neuromuscular and cognitive evaluation and rehabilitation.

### 5.1.1.2 Operating requirements

Taking into account the design of the device, its intended use and functionality, and the different functionalities proposed above, the following general requirements are established that the operation of the exercises must meet:

- The device must have a user-friendly interface, allowing independent use without constant medical supervision.
- Regarding the cognitive and motor function assessment, the device must incorporate preprogrammed tasks that allow an accurate and reliable evaluation of hand motor function and cognitive performance, while avoiding physical or mental fatigue that could affect the results of the tests.
- In addition, the device must support variations and repetitions of the programmed tasks, allowing simultaneous rehabilitation of hand motor performance and cognitive functions.
- Clinicians must have direct access to assessment data in real time, so they can assess and analyze each patient's individual progress.

With the objective of evaluating and training hand motor variables and cognitive variables, the design of the exercises is divided into two modalities: Rehabilitation and Training. Within each modality, 3 types of exercises are designed: Strength Training/Evaluation, Reaction Time Training/Evaluation, and Memory Training/Evaluation. Each exercise has a different basic functionality, which the user can know thanks to the different operation of the device's LEDs. In addition to this operation, two basic functionalities are established that all exercises had to fulfill. Firstly, the recording of data through the pressure sensors (FSRs), and secondly, the processing of this data through the microprocessor that allows knowing the user's execution and, in this way, being able to produce feedback in real time (in the case of Training Mode exercises) or store the data (in the case of Evaluation Mode). Based on that, the specific Functional Requirements (FRs) of the device are listed below:

- **FR 1 Rehabilitation:** the system will enable the necessary functionalities for motor and cognitive rehabilitation.
  - **FR 1-1 Strength training:** the system will allow strength training of the fingers (digit 2, digit 3, digit 4 and digit 5), for both hands.

- \* FR 1-1-1 Sensor registration: FSRs record every force interaction of each finger.
- \* FR 1-1-2 Data processing: The microprocessor receives and interprets the force data.
- **FR 1-2 Reaction time training:** the system will allow training the reaction speed.
  - \* FR 1-2-1 Sensor registration: FSRs will record information when pressing each finger.
  - \* FR 1-2-2 Data processing: The microprocessor will record the time between a stimulus and the user's response (pressing the FSRs).
  - \* FR 1-2-3 Data processing: The microprocessor will record if errors occur in issuing the response from the user.
- **FR 1-3 Memory training:** the system will allow training the memory.
  - \* FR 1-3-1 Sensor registration: FSRs will record information when pressing.
  - \* FR 1-3-2 Data processing: The microprocessor will record if errors occur when the user memorizes and repeats a sequence (by pressing the FSRs).
- **FR 1-4 Feedback:** the system will emit light feedback in response to user interaction in each exercise.
  - \* FR 1-4-1 Feedback in strength exercise: LEDs emit visual feedback based on the force intensity: red light for low force intensity, yellow for middle intensity, and green for high force intensity.
  - \* FR 1-4-2 Feedback in reaction time exercise: LEDs emit visual feedback based on the reaction speed: green light for fast responses (short reaction times), yellow light for medium speed responses (medium reaction times), and green light for slow responses (long reaction times).
  - \* FR 1-4-3 Feedback in memory exercise: LEDs provide visual feedback based on whether the user's answer is correct or incorrect: green light when selecting the correct answer and red light when selecting the wrong answer.
- **FR 2 Evaluation:** the system will enable the necessary functionalities for motor and cognitive evaluation.
  - **FR 2-1 Strength evaluation:** the system will allow strength evaluation of the fingers (digit 2, digit 3, digit 4 and digit 5), for both hands.
    - \* FR 2-1-1 Sensor registration: FSRs record every force interaction of each finger.
    - \* FR 2-1-2 Data processing: The microprocessor receives and interprets the force data.
  - **FR 2-2 Reaction time evaluation:** the system will allow training the reaction speed.
    - \* FR 2-2-1 Sensor registration: FSRs will record information when pressing.
    - \* FR 2-2-2 Data processing: The microprocessor will record the time between a stimulus being produced and the user's response (pressing a FSR).

- \* FR 2-2-3 Data processing: The microprocessor will record if errors occur in issuing the response from the user.
- **FR 2-3 Memory evaluation:** the system will allow training the memory.
  - \* FR 2-3-1 Sensor registration: FSRs will record information when pressing.
  - \* FR 2-3-2 Data processing: The microprocessor will record if errors occur when the user memorizes and repeats a sequence (by pressing the FSRs).
- **FR 2-4 Data storage:** the system will record and store different data in each of the exercises.
  - \* FR 2-4-1 Data in strength exercise: the system will store each measure of force of each one of the fingers, highlighting the maximum force reached by each finger.
  - \* FR 2-4-2 Data in reaction time exercise: the system will store each measurement of the reaction speed of each of the fingers, highlighting the average reaction time of each exercise.
  - \* FR 2-4-3 Data in memory exercise: the system will store the number of execution errors when repeating the memorized sequences.
- **FR 3 Warnings:** the system will notify the beginning and end of each exercise by issuing a double white flash.
- **FR 4 Change exercise:** the system will allow the user to change exercise at any time through the website.
- **FR 5 Finish:** the system will allow the end of the rehabilitation or evaluation session at any time.

## 5.1.2 Development

### 5.1.2.1 Exercises

According to the identified requirements and the use cases (rehabilitation and evaluation), the interaction of the subject with the device involves interacting with the sensors integrated in each cylinder in a different way depending on the operating mode, explained below.

#### Evaluation Mode

The Evaluation Mode (EM) of the device is designed to serve as a tool for assessing the motor status of the upper limb, specifically the hand and fingers, as well as to assess general cognitive status. The EM is characterized by recording any interaction that the user makes with the device, storing the data of interest for the evaluation, such as force (in kilograms), reaction time (in milliseconds) and execution errors, which will be explained later in this document. Through different exercises, and different levels of difficulty of each exercise, the EM of the device will allow the therapist to know the motor and cognitive state of the patients, as well as monitor their condition and progress during rehabilitation.

In the EM, the device assesses hand and finger strength through grip repetitions. Attention, reaction time, and coordination are assessed through motor responses to light indicators using specific fingers. Memory testing is done by repeating a pattern

presented through the LEDs and pressing the corresponding buttons on each finger. Finally, the patient's interaction with the device is recorded and the data is stored and transmitted to a dedicated website.

The specific tasks of the EM are explained in the following table.

<b>Evaluation Mode</b>	<b>Exercise performance</b>	<b>Recorded data</b>
Task 1: Force	The user must press the 4 finger FSRs individually or simultaneously at any time.	The device will record the force exerted every 300 milliseconds and the maximum force achieved by each finger in each interaction.
Task 2: Reaction time	The device will emit a sequence of lights while the user must press the button corresponding to each light on as quickly as possible.	The device records the time (in milliseconds) between each light turns on and the corresponding button is pressed.
Task 3: Memory	The device will emit a sequence of lights while the user must memorize it and repeat it once it has finished playing.	The device records and check if the buttons pressed are correct, counting the errors, and the force applied in each of them.

Table 5.1: Tasks and their explanation on the EM.

### Training Mode

The Training Mode (TM) of the device is designed to serve as a tool to train and rehabilitate the motor function of the upper limb, specifically of the hand and fingers, as well as to train cognitive abilities such as reaction time and memory. The TM is characterized by issuing visual feedback to the user according to the execution of the exercises. In this way, even if the patient is using the device without supervision, he will know if he is performing the exercises correctly or if, on the contrary, he is making mistakes. Different colors indicate the intensity of strength, repetition errors in sequences, or response time to stimuli. Each exercise within the training mode offers three difficulty levels.

Through different exercises, the TM of the device will allow the patient to train the individual strength of the fingers and hand grip, reaction speed and memory, being able to perform levels of greater or lesser complexity according to the individual state of each patient. The TM exercises performances are the same as those of the EM, but with the difference that the EM records all the data and the TM only gives visual feedback. The performance of the different exercises of the TM are explained in the Table 5.2.

The established intervals for force were defined as follows: low force for values from 0.01 kg to 1.5 kg, medium force from 1.5 kg to 3.5 kg, and high force for values greater than 3.5 kg. For time, the intervals were: short time for values from 0.01 seconds to 1 second, medium time from 1 second to 2 seconds, and long time for values greater than 2 seconds. These ranges were determined arbitrarily based on the pilot study, where the fastest times were used to calculate the threshold corresponding to the mean plus two standard deviations. A similar methodology was applied to the maximum force values. The resulting ranges were then divided into tertiles, providing the values used for the initial validation calculations.

These thresholds will be refined once a population sample that adequately represents all degrees of deficit and capacity is obtained, enabling a more accurate distribution of performance for each test. This process extends beyond the initial scope of validating the device's reliability.

<b>Training Mode</b>	<b>Exercise performance</b>	<b>Recorded data</b>
Exercise 1: Force	The user must press the 4 finger FSRs individually or simultaneously at any time.	Depending on the amount of force, the corresponding LED emits a colored light, distinguishing 3 grip force ranges: if the applied force is small, the corresponding LED will emit red light; if the force is high, the LED will emit green light; if the force is intermediate, the LED will emit yellow light.
Exercise 2: Reaction time	The device will emit a sequence of lights while the user must press the button corresponding to each light on as quickly as possible.	When the user presses the button, the corresponding light changes its color depending on the reaction speed: the LED will turn green if the user presses the button quickly, red if the time is long, and yellow if the time is an intermediate value between the previous established ranges.
Exercise 3: Memory	The device will emit a sequence of lights while the user must memorize it and repeat it once it has finished playing.	If the button pressed is correct, its corresponding LED will emit green light, if it is wrong, the LED will emit red light.

Table 5.2: Exercises and their explanation on the TM.

All the exercises are developed using the Python programming language. Python is a highly capable open source programming language, widely used for Big Data analysis, Machine learning, Data Science, Artificial Intelligence, but also in video games and web development. Furthermore, among its advantages is the fact that its code can be executed in any operating system, which makes it more versatile. Python allows programmers to configure the operation of the different electronic components and the raspberry to work in the way that is desired, so that it codes the specific operation of each exercise.

To be able to put the device into operation and choose the training modes and exercises, Python codes that control each exercise are integrated into an HTML website with a friendly user interface.

#### 5.1.2.2 Website

The development of the system includes a website to serve as both a controller for the device and an evaluation platform to access the recorded assessment data. The website is designed in HTML with PHP programming languages. HTML is a HyperText Markup Language widely used for the development of web applications and websites. It is used to describe the structure of a web page and organize the content. Together with PHP, both programming languages are the most used to develop web pages nowadays. PHP language is a server-side Hypertext Preprocessor, which means that it connects to and runs on a web server, not on the user/client, in addition to activating all the functional elements and the visual interface of the website. It

was decided to use PHP instead of JavaScript (another language widely used to give more functionality to HTML web pages) due to the need of integrating the website with a server that allows the connectivity between the microprocessor of the device and the website, and also the storage of device records through a database. Among the main advantages, it decreases the loading times of the website, allowing greater agility in response time and also allowing connection to large databases. Regarding the database, a MySQL server has been used that provides security mechanisms to protect the data, including authentication, authorization and encryption of communications. Users must authenticate to access the database. MySQL is widely used in web applications, content management systems, enterprise information systems, and a variety of other applications that require data storage and management. Its popularity is due to its robustness and scalability. The PHP/MySQL tandem provides the device with a secure environment that allows the user to automatically store their results in the exercises performed, being able to retrieve them on request later to evaluate their progress, in a simple way and respecting the integrity of the data.

This website allows each patient to have a private user profile where all their evaluation information is stored, as shown in Figure 5.1.

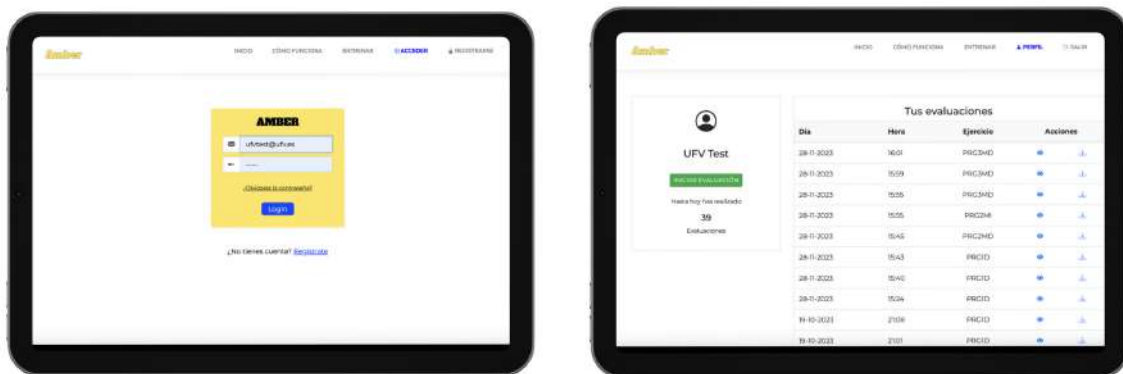


Figure 5.1: Screenshots of web interface for login and user profile.

When logged in, the website acts as a remote control, first enabling users to choose the hand (left or right as shown in Figure 5.2). Then, the user has to select the exercises and the difficulty level as desired, as shown in Figure 5.3 and Figure 5.4.



Figure 5.2: Webpage interface to select the hand for training.



Figure 5.3: Webpage interface for exercise selection for right hand training.

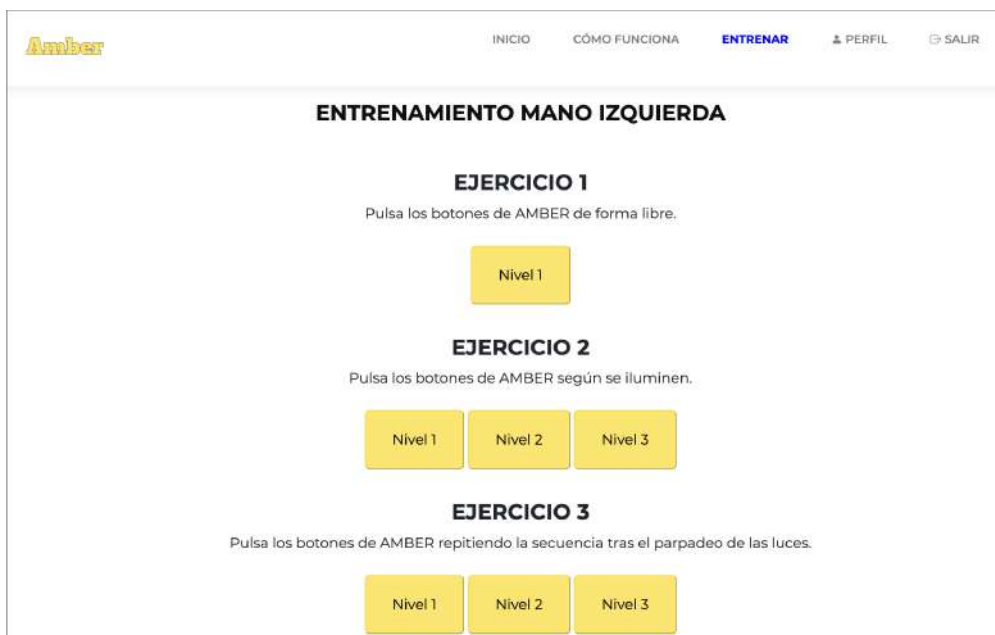


Figure 5.4: Webpage interface for exercise selection for left hand training.

The specific workflow of the device is illustrated in Figure 5.5. Upon turning on the device, users, whether clinicians or patients, access the device's website to select the working mode: Rehabilitation or Evaluation. For the Evaluation, the user first has to log in with username and password, while for Rehabilitation there is no need to do it as data will not be stored. After selecting the mode, the user chooses the exercise and desired difficulty level to be executed on the device: Exercise 1, Exercise 2 (with three

options of levels of difficulty) or Exercise 3 (with three options of levels of difficulty as well). Subsequently, the exercise is initiated on the device, and the patient performs the assigned task. Throughout the exercise on the Evaluation Mode, the device records all interactions with the sensors and stores the data in CSV format upon completion. These recorded data are then processed and transmitted to the web.

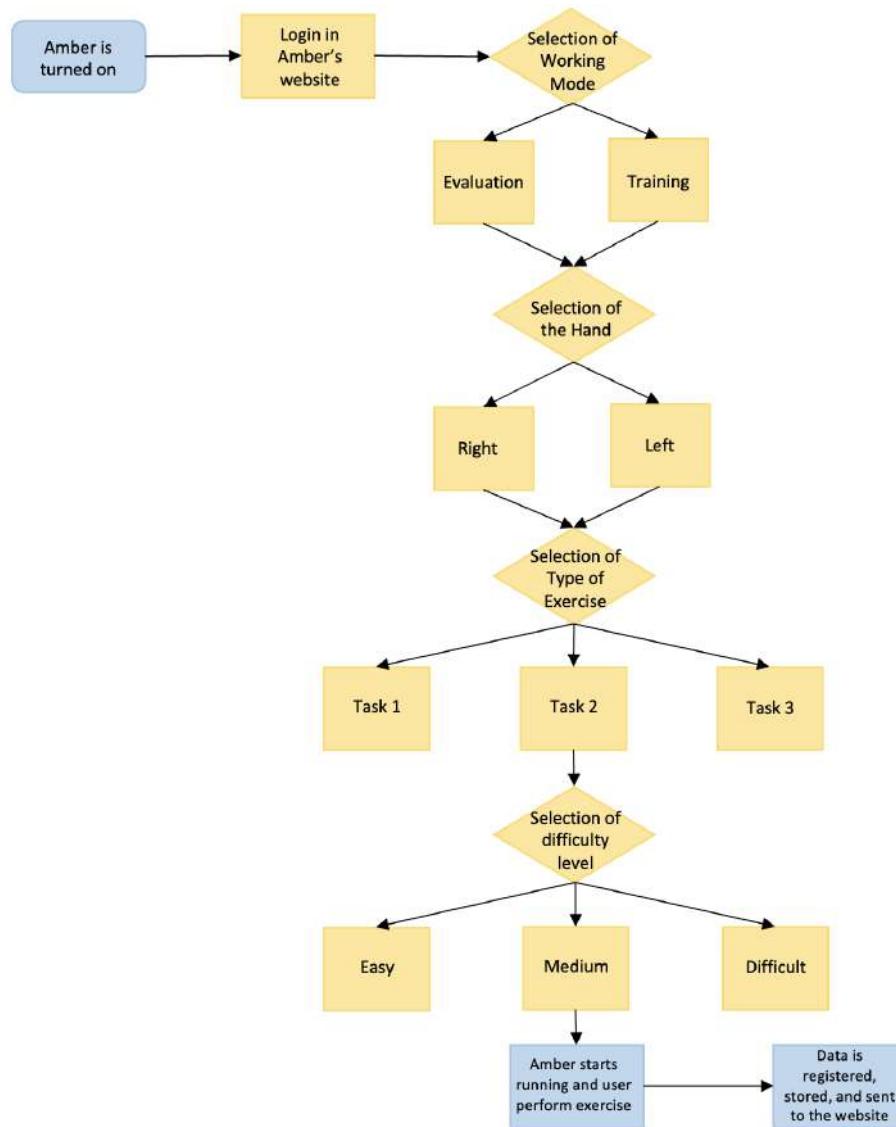


Figure 5.5: Device workflow diagram.

Additionally, the platform provides clinicians with an interface for monitoring exercise performance during training mode and the results of evaluation mode, allowing them to track patient progress, as shown in the figures below. This utility enables clinicians to remotely and in real-time assess patient evolution objectively, enabling them to optimize exercise regimens and rehabilitation sessions. Access to this information is limited to clinicians with their own private administrative accounts.

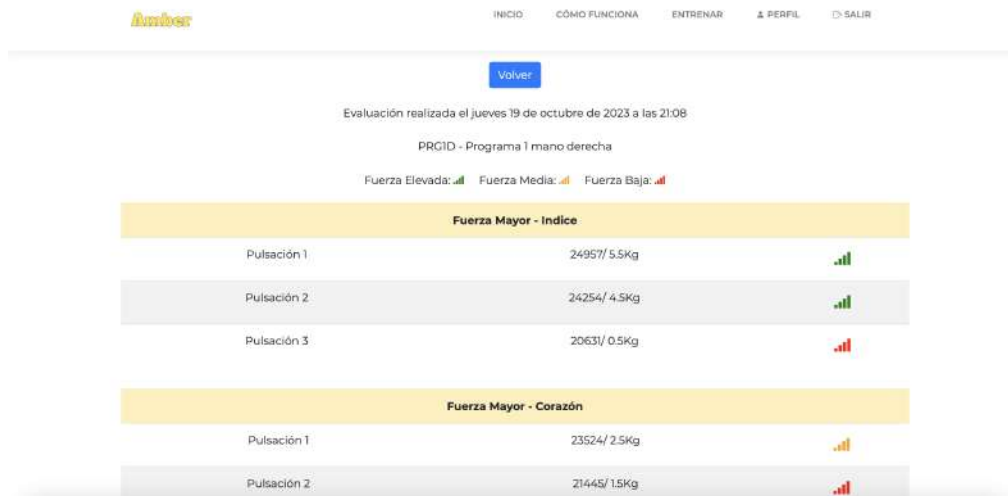


Figure 5.6: Results view of Exercise 1 (right hand) after an evaluation session.

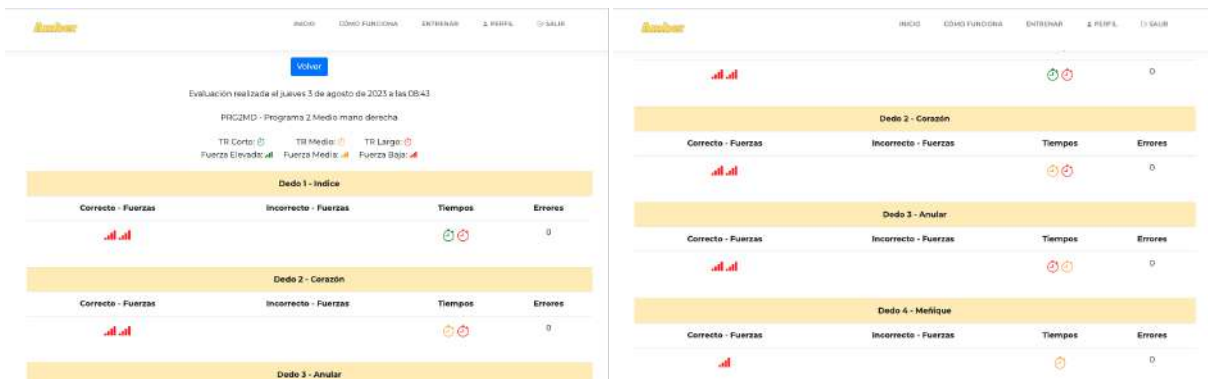


Figure 5.7: Results view of Exercise 2 - Level 2 (right hand) after an evaluation session.



Figure 5.8: Results view of Exercise 3 - Level 2 (right hand) after an evaluation session.

## 5.2 Results

The final operation of each of the exercises is explained below.

Exercise 1: the user can press the force sensors of the four fingers individually or simultaneously. Depending on the force with which each button is pressed, the corresponding LED emits a colour, this light will remain on for as long as the user is pressing the button. The colour depends on the force, so three ranges of grip force are distinguished: if a button is pressed with a small force, the corresponding LED will emit red light; if a button is pressed with a high force, the corresponding LED will emit green light; if a button is pressed with an intermediate force, the LED will emit yellow light. The change in tonality can be progressive. On the other hand, if the four buttons are pressed simultaneously with the same range of force, the four LEDs will emit a blue light. The device records and stores every interaction. The exercise will finish once each button has been pressed at least four times or if the user clicks the "Stop" button of the website. In the Training Mode, no data is recorded, while in Evaluation Mode every interaction is recorded and stored into the website.



Figure 5.9: Example of light functioning of Exercise 1.

Exercise 2: after a double flash of white light emitted by the four LEDs simultaneously (which indicates the beginning of the exercise) the device will emit blue lights one by one following a certain sequence. Once a LED turns blue, it will not turn off until the user presses its corresponding button. If the user presses an incorrect button, the device keeps the blue light waiting for the correct press. In the Training Mode, once the user presses the correct button, the blue light turns off, quickly turning green, yellow, or red, depending on how much time has been taken to press since the blue light turned on. The LED will turn green if the user presses the button quickly, it will light red if the time is long and it will turn yellow if the time to press is an intermediate value between the previous ranges. In the Evaluation Mode, the light will change into white regardless of response speed. Once the user releases the correct button, the next LED in the sequence will turn blue, following the same mechanism as just described. Once the last button in the sequence has been pressed, the device will once again emit a double white flash to indicate that the exercise has ended. In the Training Mode, no

data is record, while in Evaluation Mode every interaction is recorded and stored into the website. This exercise has three levels of difficulty:

- Easy: it is a simple sequence, without repetitions of fingers, only consecutive fingers.
- Medium: it is a sequence in which the order of some fingers is inverted.
- Difficult: in this sequence there exists finger jumps and repetitions.



Figure 5.10: Example of light functioning of Exercise 2 (similar to Exercise 3).

Exercise 3: after a double flash of white light emitted by the four LEDs simultaneously, the device will emit blue light following a defined sequence. The first LED in the sequence will turn on for two seconds, then this LED will turn off and the next LED in the sequence will turn on. This sequence will continue until the exercise is completed. The device will emit a double flash of white light from all four LEDs simultaneously to indicate that the sequence has ended. After this, the user will have to press the buttons in the same order in which the sequence of LEDs turned on. In the Training Mode, if the pressed button is correct, its corresponding LED will emit blue light, if it is incorrect, the LED will emit red light. However, in the Evaluation Mode, all the feedback light will emit in white color, regardless it is correct or not. When the user has pressed a number of buttons equal to the number of elements in the sequence, the exercise is finished. In the Training Mode, no data is record, while in the Evaluation Mode every interaction is recorded and stored into the website. This exercise has three levels of difficulty:

- Easy: it is a short sequence of 3 elements.
- Medium: it is a longer sequence of 5 elements.
- Difficult: it is a long sequence of 7 elements.

## 5.3 Discussion

The main purpose of this section was to meet the objective O3 "design a set of tests/tasks that can be carried out through the interaction with the device allowing the evaluation and training of hand motor variables and cognitive variables". The tasks proposed in this section, which meet objective O3 of this project, were satisfactorily achieved.

The design and incorporation of the specified tasks within the device are deeply based on the foundational understanding of both motor and cognitive evaluations commonly used in clinical settings. These tasks were not randomly chosen but were constructed with deliberate intent, based on a fusion of traditional methods and modern technological approaches.

### Rationale Behind Task Design

**Motor Evaluation:** One of the cornerstones of motor evaluation, especially in the context of the hand, is assessing strength. Hand strength is pivotal, not only as an indicator of muscle function but also as a predictor of functional capacity in daily life activities. This underscores the reason behind our decision to make one of the tasks revolve around measuring force. In traditional settings, tools like pinch force meters and hand dynamometers have been the gold standard. By integrating a force-measuring task in the device, we are bridging the gap between conventional and contemporary assessment tools, ensuring that the data generated remains both relevant and actionable for therapists and medical professionals.

**Cognitive Evaluation:** When it comes to cognitive evaluations, memory often stands out as a primary domain of interest. Memory, especially working memory, plays a crucial role in our daily interactions and tasks. While there are numerous tests available to evaluate memory, we chose to derive inspiration primarily from the Digit Span Test. Its simplicity and effectiveness in gauging short-term memory and attention made it a valuable model. By incorporating a memory task that uses a sequence of lights, we've modernized the traditional approach while still aiming to achieve the same evaluative outcomes. Furthermore, reaction time is a composite measure, reflecting multiple cognitive processes including attention, speed of information processing, and motor coordination. By introducing a task centered around reaction time, we encompass a wider range of cognitive faculties. Traditional tests like the Stroop Test and TMT-A have been instrumental in such evaluations. However, with the device's approach of using light sequences and immediate response mechanisms, we believe the task offers a more interactive and dynamic method to evaluate the same cognitive domains.

### Synergy with Conventional Tests

The main advantage of the device is its ability to combine conventional therapy with innovative technology. For this reason, its operation is based on similarity and alignment with established physical and neuropsychological tests, which reinforces its scientific credibility. Task design decisions were made with a two-fold objective: first, to ensure

that tasks are based on proven methodologies and, second, to take advantage of technology for a more engaging patient experience through gamification, as well as accurate data collection.

For instance, the memory task, inspired by tests like Digit Span and Corsi Blocks, offers a visually engaging alternative while still targeting the core cognitive processes. Similarly, the reaction time task, while drawing from traditional tests like the Stroop and TMT-A, provides a real-time, interactive experience for the user, potentially enhancing engagement and compliance.

### **Critical discussion**

However, it is true that the selection of these tasks focused on tests of strength and cognition that are effective for a more specific profile of post-stroke patients with a certain degree of motor and cognitive functionality. Criticism of this approach arises when considering those patients with more severe motor or cognitive impairment. Gripping capacity and interaction with cognitive exercises may be limiting for these profiles. To evaluate hand strength, alternative tests could have been considered that do not depend exclusively on grip ability, such as pressure sensors adapted to wristbands or, in other words, rehabilitation gloves, which measure strength without the need for an active grasp. This, whose current use is more widespread, would allow the inclusion of patients with considerable motor impairment who cannot grasp the device. In the cognitive domain, although memory and reaction time tasks are essential, we could have explored tests that assess other domains such as pattern recognition or sustained attention, which could be more accessible to those with advanced cognitive impairment. For example, tasks that use auditory or tactile stimuli could be more inclusive for these patients, which will be considered as future lines of research for this project, having included these qualities in the device patent.

Our internal critique highlights the need to develop a broader range of tests to accommodate varying levels of functionality. It is crucial that future research focuses on the adaptability of the device to cover a broader spectrum of post-stroke patients, and even other types of patients such as Parkinson's or Alzheimer's.

## 6. Objective 4: Validate the reliability of the device to extract motor and cognitive variables from the user

This section shows the procedure carried out to achieve objective O4, "to validate the reliability of the device to extract motor and cognitive variables from the user".

### 6.1 Methods

To achieve the objective 4 of this project a validation study was be carried out. This validation will be divided into two different studies. The first one will be a technical validation, where it will be verified that the device complies with the established functional and non-functional requirements to guarantee its correct functioning. The second validation will be performed to check if the device works as intended, analysing if its measurements are consistent and comparing its functioning with other existing devices. Both validation studies are explain through this chapter.

#### 6.1.1 Validation study

According to the Directive 2007/47/CE (RD 1591/2009) from the European Union, AMBER is a Class IIa device, which means that presents a low to moderate risk to the patient or user, as it is designed to be manipulated by patients and possess a certain amount of electrical current. In this group of devices, most rehabilitation devices and diagnostic equipment are included. Before its commercialization, different legal regulations must be taken into account that the device must comply with to obtain the CE certificate and be able to be used by the regular population. The four regulations below will be complied:

- **EU Medical Device Regulation (MDR) 2017/745:** This comprehensive regulation ensures a high level of safety and effectiveness for medical devices marketed in the EU. Emphasizes clinical evaluation, post-market surveillance and transparency, imposing strict requirements for medical device approval [254].

- **ISO 13485:** It is an international standard that specifies requirements for a comprehensive quality management system for the design and manufacturing of medical devices, focusing on consistent design, development, production, installation and delivery [255].
- **IEC 62304:** This international standard defines life cycle requirements for medical device software, focusing on software development, risk management and system validation processes to ensure safety and reliability [256].
- **Risk Management ISO 14971:** It describes a process for manufacturers to identify hazards associated with medical devices, estimate and evaluate the associated risks, control these risks, and monitor the effectiveness of the controls [257].

Taking these regulations into account, the first step is to carry out a technical validation that analyzes the functionality, robustness and efficiency of the device. After this, and prior to a clinical study with patients, a validation of the device's functionality will be carried out with a group of healthy volunteers.

#### 6.1.1.1 Technical validation

To technically validate the device, different evaluations were carried out. Firstly, the device was subjected to different stress conditions, proving to be structurally resistant and robust. Specifically, tests were carried out that consisted of forcing the device to operate by using it in a way that would not be the usual way for the patients. It has been forced to be used very quickly, pressing buttons separately and simultaneously, with very light forces and with very strong forces, without taking into account the normal use that a patient would give it, to see possible failures of the device that would have to be repaired in future steps. After some code tweaking, the device responded correctly in all tested cases. In addition, it also resisted strong pressures, not breaking or deforming, ensuring its robustness in both software and hardware. In all cases, the device recorded all interactions and responded in less than 1 second, which ensures its efficiency. Finally, its functionality was checked by performing each and every one of the exercises repeatedly and verifying that all the exercises worked correctly and correctly met all the requirements.

#### 6.1.1.2 Device validation

A medical device validation refers to the process of confirming that a medical tool (physical item or software) works as intended.

To create the best protocol to validate this new device called AMBER, we first performed an exhaustive non-systematic review of the literature. After this, we consulted 8 specialists in stroke, each with expertise in different areas (1 neurologist, 2 physiotherapists, 2 occupational therapists, and 1 neuropsychologist), all from Hospital Beata María Ana (Madrid). We had informal discussions with them, asking various questions to gather their insights and create the best evaluation protocol for testing the device's performance with subjects.

Since the device we were testing has two main functions (evaluation and training modes), we decided to focus on evaluating the device's reliability as a tool for assessing finger and hand strength, which is, the evaluation mode or EM. Additionally, we wanted to compare and see how the evaluation results correlated with some cognitive variables to see if it could be also used as a tool for evaluating general cognitive ability regarding memory and reaction time.

For this initial evaluation, we designed a study focused on healthy subjects and we planned to conduct several tests with them, so that we can establish a baseline and better understand the device's performance before moving on to test its functionality with stroke patients. Our aim was to create a comprehensive evaluation protocol that could effectively assess both motor skills and cognitive aspects. By consulting these specialists, we sought to ensure that our evaluation would be well-rounded and relevant to stroke rehabilitation.

### Evaluation protocol

To assess the device's EM, a test-retest reliability and validity study was designed and conducted. To do so, the study followed the Guidelines for Reporting Reliability and Agreement Studies (GRRAS) [258]. All procedures were in accordance with the 1964 Declaration of Helsinki and ethical approval was obtained by an independent institutional review board (N<sup>o</sup> 22/495). All participants gave written informed consent before enrollment.

Thanks to the extensive literature review carried out, and the discussions held with stroke rehabilitation specialists, the following validation protocol was established, to be carried out with 36 healthy subjects, divided into 3 evaluations explained in the subsections below: device evaluation, motor evaluation, and neuropsychological evaluation.

#### 6.1.2 Device evaluation

As this innovative device has two main working modes, first we decided to assess the device evaluation working mode with healthy subjects prior to tests its rehabilitation functionality with stroke patients. To do this, it was decided to test the three different tasks of the device (strength, reaction time, and memory exercises) by asking the 36 subjects to perform them. All device assessment were administered twice, in two different sessions, between 3 and 10 days apart to assess test-retest reliability. In each session, the 3 different preprogrammed tasks described in 5.1 were administered in all their levels of difficulty as follows.

- **Task 1: force**

Evaluates finger strength with digits 2, 3, 4, and 5 (which corresponds to the index, middle, ring, and little fingers). The subject was instructed to exert as much force as possible with each finger separately. They were verbally encouraged not to press any of the other sensors with their remaining fingers to ensure isolated measurements. The average of three attempts per finger (in kilograms) was the outcome measure.

- **Task 2: reaction time**

Assess attention and reaction time, and it offers three levels of difficulty: easy, medium, and hard. The user performed each level only once. For this task, the subject was presented with a visual stimulus, where one of the four LEDs corresponding to the four finger sensors would turn on. The subject was then instructed to respond as quick as possible by pressing the sensor corresponding to the illuminated LED using the corresponding finger. The easiest level consists of a sequence involving consecutive fingers. The difficulty increases in the medium and hard levels by introducing more challenging patterns with the omission and repetition of certain fingers. The outcome measure for this task was the average reaction time of the fingers of each hand, and it was recorded in milliseconds.

- **Task 3: memory**

Evaluates short-term memory at three difficulty levels: easy, medium, and hard. The user performed each level only once. In this task, the subject was presented with a sequence of LED lights turning on sequentially. The sequence could be of 3, 5, and 7 elements for easy, medium, and hard levels, respectively. Once the sequence was completed, the subject was asked to recall the sequence pressing the sensors corresponding to each finger in the correct order. The outcome measure for this task was the number of completely correct sequences recalled by the subject.

All tasks were performed first with the dominant hand and then with the non-dominant hand. Instructions of how to use the AMBER device and pictures of volunteers using it are shown in Appendix B.

### 6.1.2.1 Motor evaluation

In addition to the assessment of the evaluation working mode of the device, we decided to ask the same participants to perform some motor assessments to compare the results with the device. For the motor evaluation, the assessments carried on are explained below. These tests were administered only once, the same day as the first evaluation session with the device. The different assessments are explained below.

- **Conventional finger pinch force**

To assess the pinch force, subjects were asked to produce as much force as possible with each finger separately with an analog baseline hydraulic Pinch Gauge (MVS in motion, Belgium) [259], in an analogous way as it was done with the device's sensors. The average of the kilograms of force of three attempts per finger was the outcome measure. This was performed first with each finger of the dominant hand, and then with the fingers of the non-dominant hand.

- **Hand-grip strength**

Handgrip strength was assessed with a digital Jamar hydraulic hand dynamometer [260]. Subjects were asked to produce as much full-hand grip force as possible first with the dominant hand and then with the non-dominant hand. The average of the kilograms of force of three attempts per hand was the outcome measure.

- **Fine hand dexterity**

Fine manual dexterity was assessed through the Grooved Pegboard Test [261], which consists on manipulating and inserting 25 keyhole shaped pegs into the corresponding holes in the shortest possible time. It was carried out first with the dominant hand and later with the non-dominant hand. The time taken to complete the test was the outcome measure.

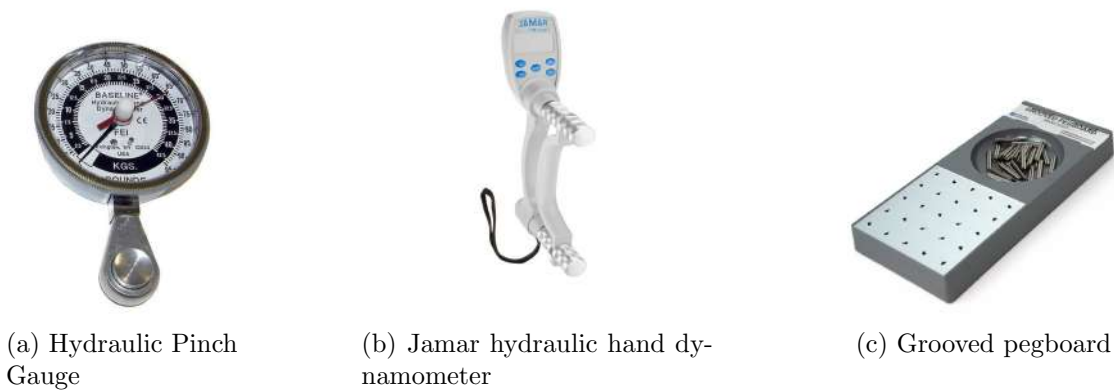


Figure 6.1: Conventional hand motor evaluation devices used.

### 6.1.2.2 Neuropsychological evaluation

A neuropsychological evaluation was also carried out, first of all to rule out participants who had mild cognitive impairment, and to compare the results of the participants with the results obtained through the device in the reaction time and memory exercises. The cognitive tests performed are explained below.

- **Processing speed (Reaction time)**

Reaction time evaluation was carried out through different computerized tasks controlled by Presentation® software (<http://www.neurobs.com>) as described elsewhere [262]. The first task was the Finger Tapping (FT), used as a measure of motor function and motor speed, providing quantitative information on slowing down of responses [263–265]. In this task, following the Strauss application norms [263], the participants were instructed to press the spacebar on the keyboard as fast as possible and repeatedly with the index finger (digit 2). Five 10-seconds attempts with each hand were performed. The average of response times (in milliseconds) recorded between 2 consecutive taps was the outcome measure of this first task. The second task, called Detection, is inspired by the SRT task of the Computerized Information Processing Testing battery [266]. This task was used as a measure of information processing speed. It is the time elapsed between the presentation of a stimulus and the execution of a motor response [267]. Participants were instructed to press the left mouse button as fast as possible when the “+” stimulus appeared in the center of the screen at varying inter-stimulus times. Just the dominant hand was used for this task. The average time between the appearance of the stimulus and the motor response was the outcome measure in this task.



Figure 6.2: Example of Detection task in Presentation software.

- **Memory**

**Immediate and working memory** was assessed through the Direct version of the Digit Span Test from Wechsler Adult Intelligence Scale-IV (WAIS-IV) [268, 269], where the subject, after hearing a sequence of numbers from the examiner, had to memorize and immediately repeat the sequence out loud trying to avoid errors. The number of completely correct sequences was the outcome measure.

**Spatial and visual memory** was tested through the Forward version of the Corsi Block-Tapping Test (CBT) [270], where the subject had to memorize and tap a sequence of blocks in the same order that the examiner had previously tapped on a subset of nine blocks. The number of completely correct sequences was the outcome measure.



(a) Digit Span Test



(b) Corsi Blocks Test

Figure 6.3: Conventional hand motor evaluation devices used.

In addition to these cognitive scales, other cognitive tests were performed to the participants in the study to analyze more different correlations and to have more data for future studies. These other cognitive scales were: MoCA, TMT (part A and part B), Symbol Digit Modality Test, and Digit-Symbol Coding Test.

### 6.1.2.3 Participants

As mentioned before, we decide to perform this evaluation protocol in a group of 36 healthy subjects. Participants were recruited among personnel of the hospital, healthy companions of patients and university students. They were included if they were adults (> 18 years) and had neither of the following exclusion criteria:

1. Presence of cognitive impairment (Montreal Cognitive Assessment < 26 points).

2. Known neurological diseases, motor or sensory disturbances that affect hand strength.
3. Visual disturbances that prevent visualizing colors such as daltonism or blindness.

Thirty-six healthy individuals participated. Their demographic characteristics are shown in Table 7.1.

Characteristics	Subjects (N=36)
Age (years)	$43.27 \pm 18.52$
Sex	
Female / Male	17 / 19
Handedness	
Right / Left	31 / 5
MoCA (score)	$28.42 \pm 1.66$

Abbreviations: MoCA: Montreal Cognitive Assessment

Data are presented as mean  $\pm$  standard deviation

Table 6.1: Socio-demographic characteristics of the participants.

The 36 participants were asked to perform the three different tasks of the device in all their levels (strength, reaction time, and memory exercises) and the motor and cognitive tests explained before.

### 6.1.3 Statistical analysis

After the evaluation of the 36 participants, the device data was extracted and the motor and cognitive tests were scored.

Statistical analyses of the data were performed using SPSS v 25.0 software (IBM Corp. Armond, NY). Specifically, the test-retest reliability of the device was analyzed to assess the stability of the measurements over time. This analysis was carried out through the Intraclass Correlation Coefficient (ICC) with a two-factor mixed model of average measures and consistency agreement. 95% confidence intervals of the ICC were obtained for measures of Tasks 1-3. ICCs were interpreted as  $< 0.5$ ,  $0.5 - 0.75$ ,  $0.75 - 0.9$ , and  $> 0.9$  for poor, moderate, good, and excellent reliability, respectively [271]. Additionally, limits of agreement were obtained by means of Bland-Altman plots, computing the difference between test and retest against the mean of the two measurements [272]. Standard Error of Measurement (SEM) was also obtained following the formula  $SEM = SD \cdot \sqrt{1 - ICC}$  [273]. Importantly, for this analysis, the data of the 36 participants were used after performing data cleaning. This cleaning consisted of eliminating outlier

values in cases in which, for the same type of measurement of a specific subject, the test and retest values differed by more than 100%.

Construct validity was analyzed to assess the accuracy with which the device measures each construct in Tasks 1-3 against a known gold standard. This was done through the Pearson correlation coefficient. Pearson's  $r$  was interpreted as showing negligible, weak, moderate, strong or very strong correlation for values 0.00-0.09, 0.10-0.39, 0.40-0.69, 0.70-0.89, 0.90-1.00, respectively [274]. For this analysis,  $\alpha = 0.05$  was set for statistical significance.

## 6.2 Results

This section shows the results of the validation study to complete the objective O4, "to validate the reliability of the device to extract motor and cognitive variables from the user", analysing the results of the evaluations.

### 6.2.1 Evaluation measurements

The 36 participants that initially enrolled the study completed both assessment sessions, with a mean interval of  $6 \pm 1.89$  days between test and retest. Missing data for at least one task and session were present in 4 participants.

The following two tables show the measurements carried out on the first day of evaluation. Table 6.2 shows the measurements relative to the strength evaluations, first with the Device, and then with the Pinch Gauge, the hand dynamometer, and the Grooved Pegboard test. Table 6.3 shows the measurements related to the reaction time and memory assessments, first the ones performed with the device and then with the Presentation software, the Direct version of the Digit Test from Wechsler Adult Intelligence Scale-IV (Digits-D WAIS-IV) and the Corsi Block-Tapping Test (CBT).

In addition to these values, measurements of all device tasks were again obtained on a second day, so that test-retest reliability can be evaluated, the data and results of which are presented in the next section.

Variable	Measurements day 1	
	Mean	SD
<b>Pinch Force - Device (kg)</b>		
Dominant side		
Digit 2	4.76	1.12
Digit 3	3.13	1.19
Digit 4	2.29	1.08
Digit 5	1.37	0.76
Non-dominant side		
Digit 2	3.58	1.25
Digit 3	2.99	1.06
Digit 4	1.92	0.98
Digit 5	1.88	1.16
<b>Pinch Force - Pinch Gauge (kg)</b>		
Dominant side		
Digit 2	4.71	1.22
Digit 3	4.10	1.21
Digit 4	3.11	1.15
Digit 5	1.94	0.92
Non-dominant side		
Digit 2	4.32	1.29
Digit 3	4.00	1.29
Digit 4	2.82	1.17
Digit 5	1.97	0.91
<b>Grip Strength - Dynamometer (kg)</b>		
Dominant hand	28.52	10.26
Non-dominant hand	25.38	8.98
<b>Fine hand dexterity – Grooved Pegboard (sec)</b>		
Dominant hand	64.83	16.52
Non-dominant hand	71.26	18.07

Abbreviations: SD, standard deviation; kg, kilograms; sec, seconds.

Table 6.2: Measurements done the first day of evaluations (first part).

Variable	Measurements day 1	
	Mean	SD
<b>RT – Device (msec)</b>		
Dominant side - overall	695.42	131.86
Digit 2	674.14	111.03
Digit 3	719.83	181.00
Digit 4	704.28	167.00
Digit 5	687.86	172.32
<b>RT – Presentation (msec)</b>		
Tapping		
Dominant side	164.85	24.11
Non-dominant side	185.21	31.25
Mean sides	173.93	26.50
Detection	281.89	30.46
<b>Memory – Device</b>		
Score	3.83	1.34
<b>Memory – Digits-D WAIS-IV</b>		
Score	4.53	1.11
<b>Memory – CBT</b>		
Score	4.47	1.16

Abbreviations: SD, standard deviation; RT, Reaction Time; sec, seconds; msec, milliseconds; Digits-D WAIS-IV, Direct version of the Digit Test from Wechsler Adult Intelligence Scale-IV; CBT, Corsi Block-Tapping Test.

Table 6.3: Measurements done the first day of evaluations (second part).

### 6.2.2 Test-retest device reliability

Reliability and SEM results for each Task and finger, are shown in Table 6.4, to test the feasibility of the measurements of the device comparing the data obtained in two different days of evaluations. Limits of agreement analysis is shown in Figure 6.4, Figure 6.5 and Figure 6.6.

Variable	Device Test (day 1)		Device Test (day 2)		ICC (95% CI)	SEM
	Mean	SD	Mean	SD		
<b>Task 1 - Strength (kg)</b>						
Dominant side						
Digit 2	4.76	1.12	3.97	1.52	0.741 (0.470-0.874)	0.570
Digit 3	3.13	1.19	3.13	1.25	0.801 (0.611-0.899)	0.531
Digit 4	2.29	1.08	2.07	1.05	0.786 (0.572-0.893)	0.500
Digit 5	1.37	0.76	1.24	0.67	0.784 (0.563-0.893)	0.353
Non-dominant side						
Digit 2	3.58	1.25	3.15	1.43	0.851 (0.704-0.925)	0.483
Digit 3	2.99	1.06	2.73	1.38	0.784 (0.572-0.891)	0.493
Digit 4	1.92	0.98	1.89	1.25	0.852 (0.707-0.925)	0.377
Digit 5	1.88	1.16	1.53	1.06	0.814 (0.619-0.909)	0.500
<b>Task 2 - RTs (msec)</b>						
<b>Average of levels</b>						
Dominant side *						
Digit 2	695.42	131.86	615.08	123.54	0.782 (0.568-0.890)	61.57
Digit 3	674.14	111.03	647.06	106.77	0.715 (0.441-0.855)	59.27
Digit 4	719.83	181.00	618.80	117.78	0.754 (0.518-0.875)	89.77
Digit 5	704.28	167.00	625.74	141.84	0.863 (0.728-0.931)	61.81
Non-dominant side *						
Digit 2	689.03	140.55	657.00	136.19	0.833 (0.668-0.916)	57.44
Digit 3	627.97	145.18	649.80	99.24	0.786 (0.580-0.891)	67.16
Digit 4	668.42	185.10	669.86	135.89	0.740 (0.491-0.868)	94.38
Digit 5	695.75	110.17	675.60	118.77	0.885 (0.772-0.942)	37.36
<b>Easy level</b>						
Dominant side *	679.39	170.43	627.76	128.54	0.707 (0.420-0.852)	92.253
Non-dominant side *	669.59	177.55	630.50	171.21	0.684 (0.373-0.840)	99.808
<b>Medium level</b>						
Dominant side *	661.17	100.99	623.10	127.13	0.805 (0.610-0.903)	44.596
Non-dominant side *	686.97	161.49	659.59	137.94	0.718 (0.442-0.858)	85.757
<b>Hard level</b>						
Dominant side *	756.36	130.00	657.22	126.53	0.696 (0.392-0.848)	71.677
Non-dominant side *	725.90	175.38	686.96	130.78	0.554 (0.107-0.777)	117.124
<b>Task 3 - Memory</b>						
Score	3.83	1.34	4.53	1.23	0.774 (0.556-0.885)	0.637

Abbreviations: SD, standard deviation; kg, kilograms; RT, Reaction Time; msec, milliseconds; ICC, Intraclass Correlation Coefficient; CI, confidence interval; SEM, standard error of measurement.

\* Overall.

Table 6.4: Measurements done the first day (test) and the second day (retest) of evaluations.

Plots in Figures 6.4, 6.5 and 6.6 show the difference between test and retest against the mean of the two days, for strength (data in kilograms), reaction times (data in milliseconds) and memory (score), respectively. The mean difference (solid black line) and upper and lower limits for a 95% confidence interval (dashed blue lines) are shown. Each dot represents a single participant.

As shown in table 6.4, in Task 1 (strength),  $ICC = 0.741-0.852$  showed moderate to good test-retest reliability. The device was slightly more reliable with the non-dominant than the dominant hand ( $ICC = 0.784-0.852$  vs  $ICC = 0.741-0.801$ , respectively). Accordingly, SEM was higher for the dominant hand compared to the non-dominant side ( $SEM = 0.353-0.570$  kg vs  $SEM = 0.377-0.500$  kg, respectively). As can be seen in Figure 6.4, most of the participants are within the limits of the 95% confidence interval, so the limit of agreement was considered satisfactory.

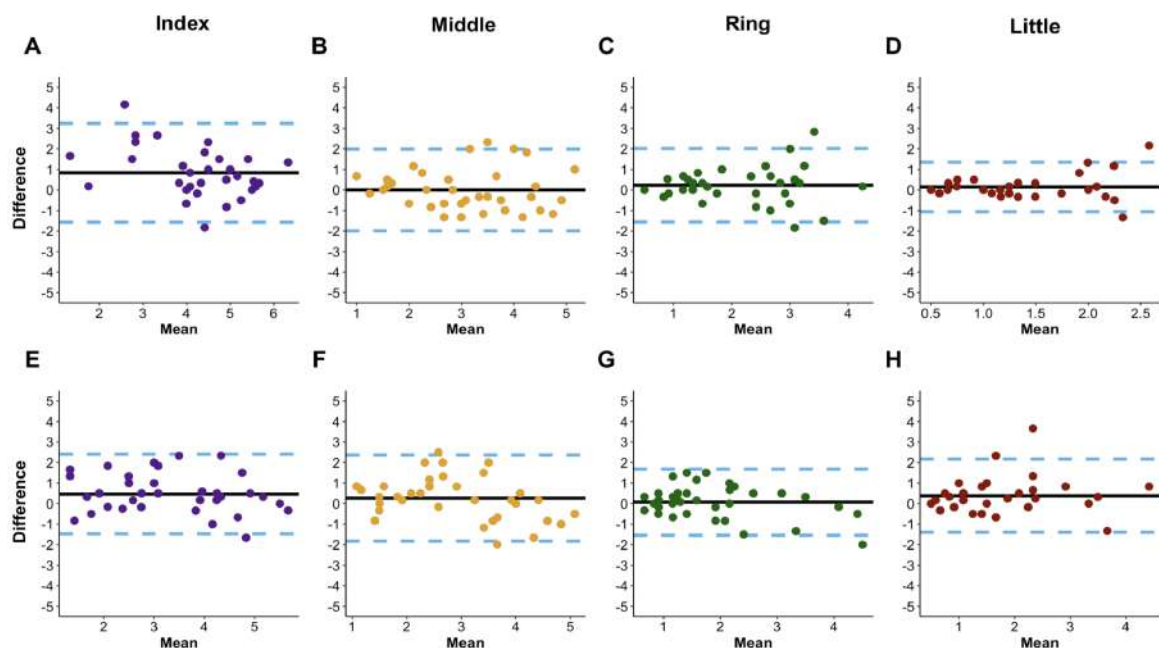


Figure 6.4: Bland-Altman plots for finger strength. Panels A-D and E-H show the finger strength of the dominant and non-dominant hand, respectively.

In Task 2 (reaction time),  $ICC = 0.715 - 0.90$  showed moderate to good test-retest reliability. In this case, the device was also slightly more reliable with the non-dominant than the dominant hand ( $ICC = 0.74-0.90$  vs  $ICC = 0.715-0.863$ , respectively). Accordingly, SEM was higher for the dominant hand compared to the non-dominant side ( $SEM = 0.059-0.090$  sec vs  $SEM = 0.037-0.094$  kg, respectively). The 95% confidence interval was also considered satisfactory in this case, since, as can be seen in Figure 6.5, the values of almost all the participants are within this range.

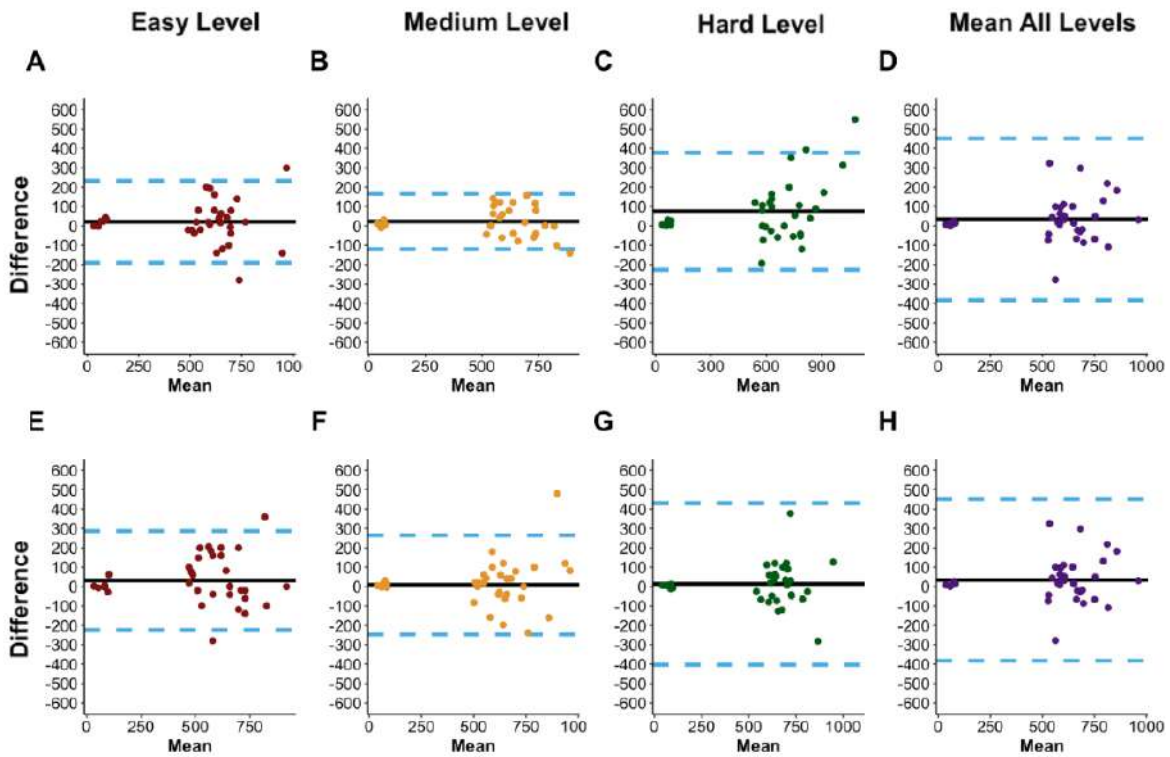


Figure 6.5: Bland-Altman plots for RTs. Panels A-D and E-H show the dominant and non-dominant hand respectively, for each of the levels (easy, medium and hard) and for the average of the three levels.

In Task 3 (memory),  $ICC = 0.774$  showed good test-retest reliability. As seen in Figure 6.6, in this case also the values of the majority of the participants are within the established 95% confidence interval.

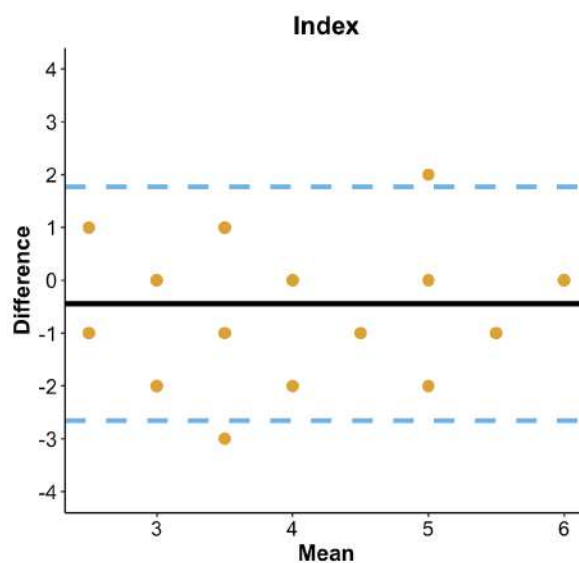


Figure 6.6: Bland-Altman plot for memory.

### 6.2.3 Motor validation

In addition to the test-retest reliability study, motor data were analyzed through two more different strategies. First, a construct validity analysis to correlate the finger strength measured by the device to the finger strength measured by pinch guage as a "gold standard". Secondly, a criterion and convergent analysis to correlate the **strength measurements done by the devices** and to the fine manual dexterity measured by the Grooved Pegboard test, respectively.

#### 6.2.3.1 Construct validity

Correlation analysis between each Task and conventional evaluation of finger pinch force are shown in Table 6.5.

The finger Pinch Gauge used in this project is an analogue hydraulic Pinch Gauge, whose operation is based on a hydraulic principle to measure the applied force. Its measurements are presented by means of a measurement scale in kilograms, with half-kilogram increments between each graduated mark.

In Task 1 (strength), the device showed moderate to strong correlations with its pinch force counterparts (Pearson's  $r$  range: 0.563 to 0.781, all P-value  $< 0.001$ ). Comparable correlations between the device and pinch force were found across fingers in each hand, and in finger pairs (i.e., index-index) across hands.

Device	Pinch Gauge	
	Pearson's $r$	P-value
Dominant side		
Digit 2	0.766	$< 0.001$
Digit 3	0.597	$< 0.001$
Digit 4	0.563	0.001
Digit 5	0.671	$< 0.001$
Non-dominant side		
Digit 2	0.781	$< 0.001$
Digit 3	0.648	$< 0.001$
Digit 4	0.744	$< 0.001$
Digit 5	0.756	$< 0.001$

Table 6.5: Correlation results of the force measured by Device and the Pinch Gauge.

The following images show the correlation matrix of the measurements of the AMBER Device and the Pinch Gauge, differentiating by finger, both for the dominant and non-dominant hand.

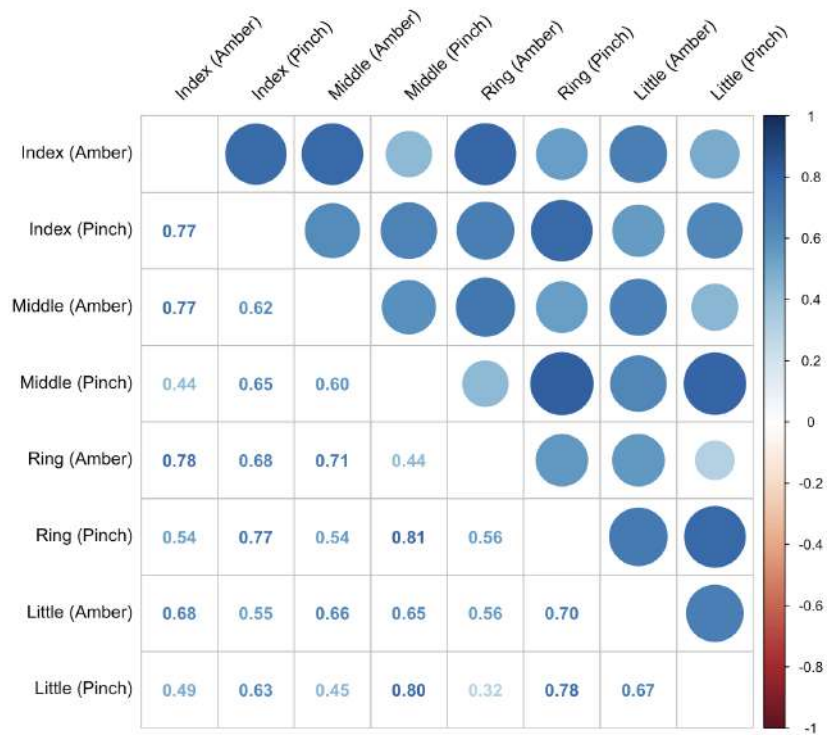


Figure 6.7: Correlation matrix between Device and Pinch Gauge for the dominant hand.

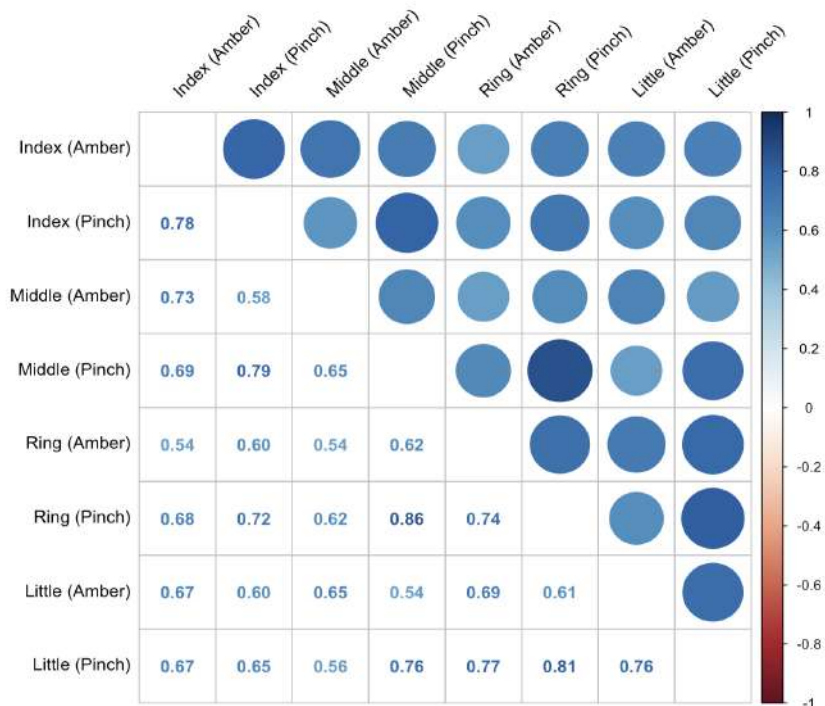


Figure 6.8: Correlation matrix between Device and Pinch Gauge for the non-dominant hand.

### 6.2.3.2 Criterion and convergent validity

#### Criterion validity

Finger strength measurements done by the devices were correlated to hand grip strength measure by an hydraulic hand dynamometer, both ways to measure gross manual dexterity, one through individual finger strength and the other through whole-hand grip strength.

Device		Dynamometry	
		Pearson's r	P-value
Dominant (overall strength)	hand	0.159	0.410
Non-dominant (overall strength)	hand	0.597	0.001

Table 6.6: Correlation results between strength measures done with device and dynamometry test.

In Task 1 (strength), the device showed a moderate correlation analyzing the validity of criteria when comparing the finger strength tasks of the device with a similar but different construct such as grip strength measured with a dynamometer.

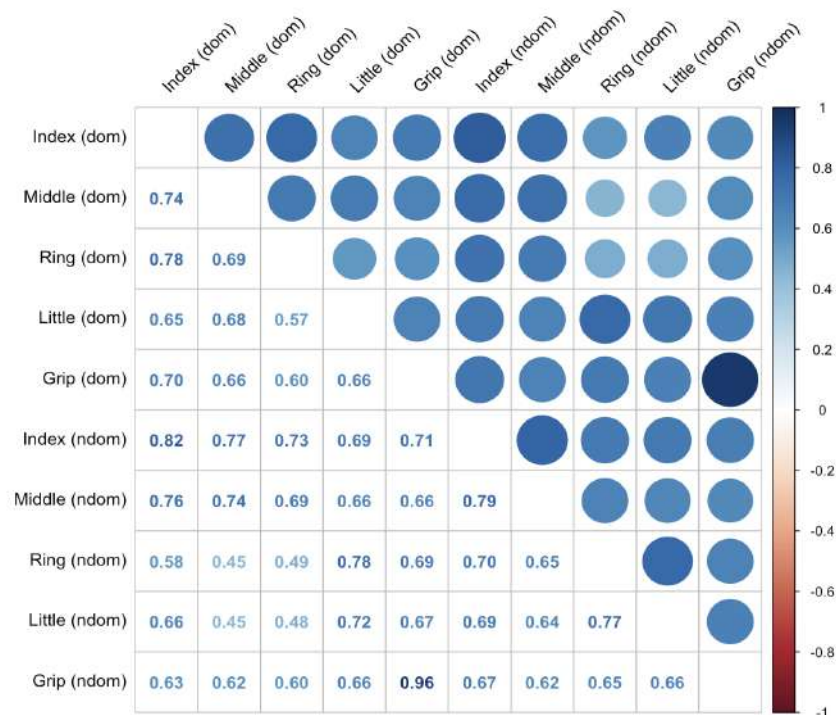


Figure 6.9: Correlation matrix between Device and Pinch Gauge for both hands including hand grip strength measured by the dynamometer.

### Convergent validity

Finger strength measurements done by the devices were correlated in this case to measurements of fine manual dexterity through the Grooved Pegboard Test.

Device		Grooved Pegboard	
		Pearson's r	P-value
Dominant	hand	0.597	0.001
(overall strength)			
Non-dominant	hand	0.298	0.116
(overall strength)			

Table 6.7: Correlation results between strength measures done with device and Grooved Pegboard Test.

In Task 1 (strength), no convergent validity was found when comparing the measurements of the device with the final manual dexterity task of the Grooved Pegboard, being totally different and conceptually distant constructs.

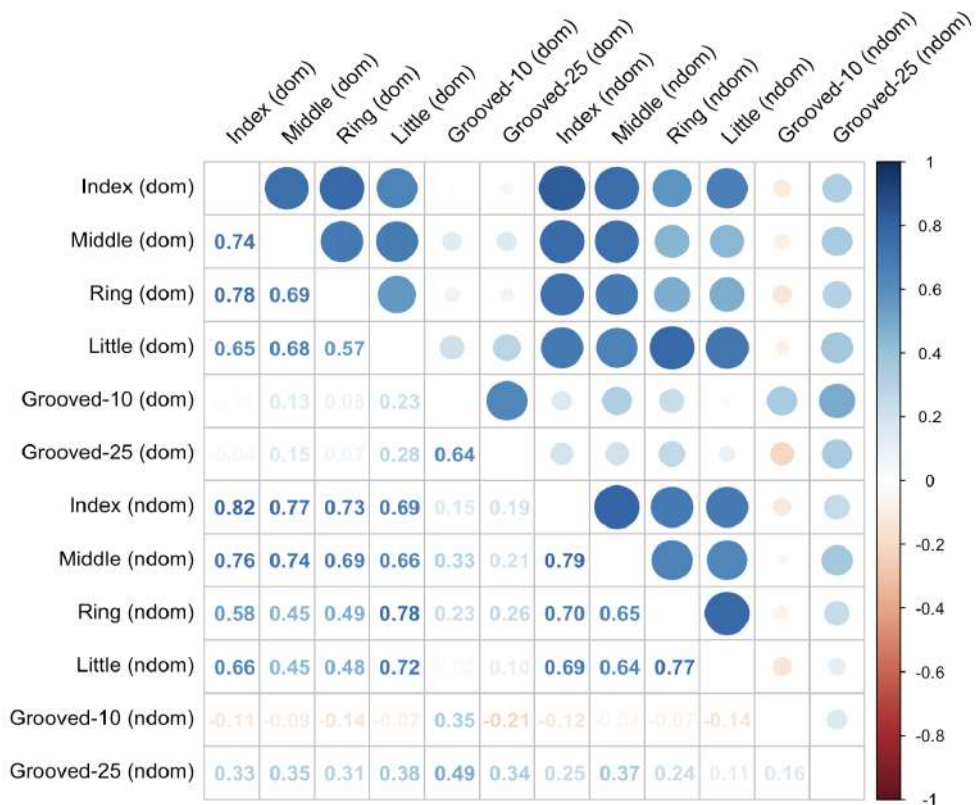


Figure 6.10: Correlation matrix between Device and Pinch Gauge for both hands including values of Groveed test for 10 seconds and for 25 seconds.

## 6.2.4 Cognitive validation

### 6.2.4.1 Construct validity

In Task 2 (reaction time), the device showed weak to strong correlations with the computerized finger tapping, varying with respect to the level of difficulty of the task, obtaining higher correlations as the difficulty of the exercise increases (Pearson's  $r$  range: 0.383 to 0.702, all  $P$ -value  $< 0.05$ ). Comparable correlations were found between the device and the detection task, higher correlations were seen comparing the hardest level of the device and also comparing the average value of all the 3 difficulty levels of the task for both hands with the computerized task.

Device	Tapping		Detection	
	Pearson's $r$	P-value	Pearson's $r$	P-value
<b>Average of levels</b>				
Dominant side*	0.592	$< 0.001$	0.373	0.025
Non-dominant side*	0.649	$< 0.001$	-	-
<b>Easy Level</b>				
Dominant side*	0.383	0.021	0.138	0.422
Non-dominant side*	0.444	0.007	-	-
<b>Medium Level</b>				
Dominant side*	0.447	0.006	0.334	0.006
Non-dominant side*	0.426	$< 0.001$	-	-
<b>Hard Level</b>				
Dominant side*	0.592	$< 0.001$	0.422	$< 0.001$
Non-dominant side*	0.702	$< 0.001$	-	-

\* Overall.

Table 6.8: Correlation results of the reaction times measured by device and the Presentation software: Tapping and Detection.

In Task 3 (memory), the device showed moderate correlations with the direct version of the Digit test from WAIS-IV (Pearson's  $r$ : 0.637,  $P$ -value  $< 0.001$ ). To calculate this correlation, since the memory exercise of the device has 3 levels of difficulty with memorization of sequences of 3, 5 and 7 digits, we used a subscore of the Digits test, comprising only the sequences of 3, 5 and 7 digits among all those in the test. On the other hand, the Task 3 of the device showed a weak correlation with the forward version of the Corsi Block-Tapping Test (CBT), which was not statistically significant (Pearson's  $r$ : 0.236,  $P$ -value = 0.116).

Memory	Digits-WAIS		CBT	
	Pearson's r	P-value	Pearson's r	P-value
Score	0.637	< 0.001	0.236	0.166

Abbreviations: WAIS, Wechsler Adult Intelligence Scale; CBT, Corsi Block-Tapping Test.

Table 6.9: Correlation results of the Memory scores measured by device and the Direct version of the Digit Test from WAIS-IV, and also the Forward version of the CBT.

#### 6.2.4.2 Other cognitive analysis

The cognitive variables related to reaction times and memory analyzed in the previous subsection were analyzed first as they were the most similar to the device exercises. The analyses of the other cognitive variables are shown in the following tables. To do this, tasks whose results are the execution time of the task will be separated from tasks whose results are the score obtained.

Device	TMT-A		TMT-B	
	Pearson's r	P-value	Pearson's r	P-value
Dominant hand – overall RT	0.421	0.011	0.572	< 0.001
Non-dominant hand - overall RT	0.434	0.008	0.439	0.007

Abbreviations: TMT, trial making test.

Table 6.10: Correlation results between reaction times measured by device and cognitive tests related: TMT-A and TMT-B.

In Task 2 (reaction time), moderate correlation was found between the mean value of reaction times of the right and left hand, with respect to the time taken to perform the TMT-A and TMT-B tasks, with better correlation with TMT-B. This results are shown in Table 6.10.

Device	Stroop W		Stroop C		Stroop WC	
	Pearson's r	P-value	Pearson's r	P-value	Pearson's r	P-value
Memory Score - Test	0.430	0.009	0.376	0.024	0.404	0.014
Memory Score - Retest	0.564	0.000	0.522	0.001	0.392	0.018

Abbreviations: W, Words; C, Colors; WC, Words-Colors.

Table 6.11: Correlation results between memory scores measured by the device and related cognitive tests.

Device	Stroop Interference		SDMT		DSCT	
	Pearson's r	P-value	Pearson's r	P-value	Pearson's r	P-value
Memory Score - Test	0.279	0.099	0.344	0.040	0.390	0.019
Memory Score - Retest	0.078	0.649	0.391	0.018	0.520	0.001

Abbreviations: SDMT, Symbol Digit Modality Test; DSCT, Digit-Symbol Coding Test.

Table 6.12: Correlation results between memory scores measured by the device and more related cognitive tests.

In Task 3 (memory), weak and moderate correlations were found in different convergent validity analysis between the memory scores of the device, and different cognitive test related: Stroop, SDMT and DSCT. This results are shown in Table 6.11 and Table 6.12.

## 6.3 Discussion

Once the device and its tasks had been developed, meeting the objective O4, "to validate the reliability of the device to extract motor and cognitive variables from the user". For this validation, a protocol was design and established with a group of healthy adult volunteers to assess the technical capabilities and reliability of the device as a motor and cognitive assessment tool. These subjects participated in two testing sessions on different days. On the first day they used the AMBER device and all the different tasks and levels it contains, as well as performing a series of motor and cognitive assessments with which to compare the data. On the second day they used only the AMBER device, so that the test-retest reliability of the device could be analyzed.

After in-depth analysis, the device demonstrates technical capabilities that allow the desired assessments to be made with minimal error at steady state. In addition, the accuracy of their mode of assessment was thoroughly tested. It can measure the precise force exerted with each finger and can provide an assessment of various cognitive functions that could be used to assess processing speed, attention, and memory. The Test-Retest reliability for the three measures (strength, reaction time and memory) shows moderate to good results. The results of this preliminary study conducted with healthy subjects are discussed below.

### 6.3.1 Strength

Strength measurements of each finger were performed with the AMBER device on two different days to analyze Test-Retest reliability. In addition, on the first day of measurements, other gross force measurements of each finger were made with the Pinch Gauge as the gold standard, hand grip strength with the dynamometer, and fine manual dexterity measurements through the grooved test.

In the first place, it is observed how the measurements of the strength of each finger show the same tendency, both measured with AMBER and with the Pinch Gauge. The finger that exerts greater force is digit 2, followed by digit 3, then digit 4, and the finger that exerts less force is digit 5. Furthermore, this trend is shown for both the dominant and non-dominant hands. These results are in line with those of other studies, such as [275], where regardless of gender and age, the finger that performs the greatest force is digit 2, followed by digit 3, digit 4, finally the one that exerts the least force is digit 5.

Regarding the test-retest analyses, strength measures show good reliability for 7 of the 8 fingers, where intraclass correlation reliability coefficients were high ( $> 0.75$ ) except for the digit 2 of the dominant hand (with an ICC = 0.741). The reason behind this lower reliability is likely attributed to the notably higher strength values recorded for the dominant hand's digit 2 on the first day compared to the second day. This discrepancy is possibly due to the testing protocol, where all evaluations began with the digit 2 first, followed sequentially by the other fingers, without providing the option of a first familiarization trial. Subjects, when confronted with this new device, might have felt uncomfortable during the initial grasp of the device with their digit 2. Several of them commented that they found it more comfortable to perform the exercises on the second day. In addition, the evaluated person observed how the subjects took longer to adjust the device to their size on the first day and how sometimes the device even slipped out of their hands, something that only happened on the second day. This discomfort in the grip may have been the reason why they did not exert force in the same way on both days. However, as they progressed to the second day, familiarization with the grip of the device and the specific way they needed to press each finger may have led to more consistent force measurements for finger 2. In addition, the need for familiarization may also be the reason why the correlation has better results with the dominant hand than with the non-dominant hand, since the exercises were always performed first with the dominant side.

In terms of correlation analysis, the correlation between AMBER's measured finger strength and her "gold standard" Pinch Gauge showed a moderate to good correlation (Pearson's  $r$  range: 0.563 to 0.781), with the finger with the least correlation was digit 4 of the dominant hand and those with the highest correlation were digit 2 of the dominant and non-dominant hand. This may also be due to the fact that they need to familiarize themselves with the device, since the subjects showed greater problems when grasping both instruments with the digits 4 and 5 (ring and little finger) than with the rest, and also due to the weakness of the fingers. digits 4 and 5 when grabbing an object, as demonstrated by [276].

On the other hand, the correlation of the force values of each finger measured with the AMBER device and the value of grip force measured with the dynamometer was analyzed. The mean strength values for each finger of each hand show a moderate correlation with the grip strength of each hand. In addition, it can be seen how a very similar relationship is maintained between the correlation of the individual strength of each finger with respect to the grip of that hand, and the correlation between AMBER and the Pinch Gauge (where the finger with the least correlation is the digit 4 of the dominant hand and those with the highest correlation being the digit 2 of the

dominant and non-dominant hand), which demonstrates the consistency of AMBER's measurements.

However, no convergent validity was found when comparing device measurements with the final Grooved Pegboard manual dexterity task. This fits the purpose of the device, as AMBER performs gross force measurements, such as the Pinch Gauge and dynamometer, while the Grooved Pegboard test measures ultimate manual dexterity, an entirely different and conceptually distant construct.

### 6.3.2 Processing speed (reaction time)

In terms of the reliability of reaction times, there is a moderate to good correlation between the test and retest results. To calculate this correlation, we averaged the reaction times of each finger at each level of difficulty. Reaction time is a measure of how quickly our brain processes information and responds to it. It includes several components, such as the time it takes to detect a stimulus and the time it takes to produce a motor response. In between, there are complex cognitive processes that happen in a graded manner. The simplest task is the finger tapping task, where no cognitive processing is involved. This task allows us to directly evaluate motor skills. Our device has not a directly equivalent task. In more complex tasks, participants need to detect a stimulus and respond to it while sensory and motor components interact. Lastly, in tasks where the response is done with just one finger while inhibiting the rest, inhibitory control is expected to be involved. This complex process is expected to be the most similar to the second task of our device. For the analysis of the results of the assessment with the device, we did not differentiate the finger that executed the response. This is because we cannot control the different motor control capabilities of each finger, as they largely depend on individual differences among participants. Among the three levels of difficulty, the medium level demonstrates the highest reliability (ICC = 0.805 with the dominant hand and ICC = 0.718 with the non-dominant hand). While one might assume that the reliability would decrease as the level of difficulty increases, in this case, the easiest level actually exhibits lower reliability than the medium level. This could be attributed to the fact that subjects didn't undergo any training trial, and the easy level helps them understand the exercise dynamics better. Regarding the hardest level, the lower reliability could be due to a greater increase in difficulty than intended, leading subjects to face a more challenging task compared to the transition from the first level to the second. Furthermore, at all difficulty levels, a decrease in reaction time is observed during the retest compared to the initial test. This suggests that subjects become more familiar with and learn the exercises over time during the first assessment. Regarding the correlation with the computerized evaluation of reaction times, it is worth specifying the two reaction time constructs we used: tapping, which is a simple motor task with no cognitive processing involved, and detection, a complex cognitive task involving sensory and motor elements. We only evaluated the detection construct using the dominant hand, as assessing the non-dominant hand could introduce unexpected motor variables due to the ease of using the computer mouse.

Overall, we observed significant positive correlations between the device's measurements and both tapping and detection reaction times. On the dominant side, the de-

vice's measurements showed a moderately strong correlation with tapping (Pearson's  $r$  range: 0.383 to 0.592) and a relatively weaker correlation with detection (Pearson's  $r$  range: 0.138 to 0.422). These correlations were statistically significant for all difficulty levels. On the non-dominant side, we also observed significant positive correlations between the device's measurements and tapping (Pearson's  $r$  range: 0.426 to 0.702).

Regarding the different levels of difficulty, the correlations remained consistent with the overall trend. At the easy level, the device's measurements exhibited a moderate correlation with tapping on both dominant and non-dominant sides. However, for the detection task, the correlations were weaker and non-significant, which suggests that the device's measurements might be more reflective of simple motor tasks rather than complex cognitive tasks at this level.

Moving to the medium level, the correlations between the device's measurements and tapping were statistically significant on both dominant and non-dominant sides. The same occurred for the detection task. The strength of the correlations increased compared to the easy level, indicating that the device's measurements captured variations in both simple motor tasks and complex cognitive tasks more effectively at this level.

At the hard level, the correlations between the device's measurements and tapping on both sides were strong and statistically significant. The correlation with the detection task was also better than at the moderate level.

In summary, the results suggest that our device's capability to measure reaction times is positively correlated with both tapping (simple motor task) and detection (complex cognitive task) across different difficulty levels. The device appears to be more sensitive to simple motor tasks' reaction time overall and shows stronger correlations compared to complex cognitive tasks, especially at easier levels. These findings may reflect that the response to easiest levels is done in an automatic manner, similarly to the tapping paradigm in computerized evaluation, as the cadence of appearance of the stimulus is constant, so the activation of complex cognitive processes is not needed. When more complex sequences are presented, the reaction times increase. The poorer correlation might be justified by the fact that the stimulus presentation in the computerized detection task is variable, whereas in our device, it is done at a regular frequency, just varying the location of the stimuli.

### 6.3.3 Memory

Memory exercises of the device show good reliability and demonstrates a strong positive correlation when compared to conventional evaluations as a subscore of the direct version of the Digit test from WAIS-IV, despite the auditive learning paradigm used in that test. Our device utilizes different stimulus locations that need to be memorized, leading us to also employ the forward version of the CBT for comparison. However, the correlation with CBT was not statistically significant (Pearson's  $r$ : 0.236,  $P$ -value = 0.116). This lack of significance may be attributed to the fact that fingers are often associated with numerical symbols, and their memorization might be following the phonologic learning pathway, similar to the digits test, rather than the CBT.

## **7. Objective 5: Determine the usability of the device by therapists specialized in rehabilitation**

This chapter reflects the usability study carried out among therapists specialized in stroke rehabilitation and the healthy volunteers participating in the validation process.

### **7.1 Methods**

To proceed with the usability study of the new device developed during this project, we performed two different types of usability studies: one focused on therapists specialized in stroke rehabilitation, and other focused on the healthy volunteers who used the device for the validation. Both studies served to obtain the opinion and feedback, on firstly from rehabilitation specialists who could give us a realistic opinion about the clinic utility of this device, and secondly from users who, although they were not the end user profile, used the device the same way that a patient would. This allowed them to share their experience using the device in terms of complexity of use and ergonomics, as in other studies evaluating the usability of new assessment and rehabilitation tools through therapists and healthy subjects [277, 278]. As highlighted in these studies, evaluating rehabilitation or assessment devices through the interaction of healthy users and specialists is an approach that allows for a thorough evaluation of the clinical utility and ergonomics of the device. For this reason, therapists are sought to provide a realistic perspective on clinical applicability, while volunteers provided feedback on the complexity of use and ergonomics of the device.

#### **7.1.1 Usability study with stroke therapists**

The main objective of the usability study carried out with specialized rehabilitation therapists was to know if they consider this device is useful for the evaluation and rehabilitation of stroke patients.

To do this, a group of 16 therapists from Hospital Beata María Ana (Madrid) were recruited, including physiotherapists, neuropsychologists, occupational therapists and neurologists, all of them specialized in treating stroke patients.

The following table shows the characteristics of the participants.

Participant	Age (range)	Speciality	Years of EXP (range)	FAM with tech. devices	Use of tech. devices in clinic
P1	18-29	Neurophysio.	1-5	3/10	8/10
P2	40-49	Neurophysio. and OT	16-20	9/10	7/10
P3	30-39	OT	6-10	9/10	8/10
P4	40-49	Neuropsychol	16-20	6/10	7/10
P5	30-39	Physio. and OT	1-5	5/10	5/10
P6	30-39	Neuropsychol.	1-5	7/10	5/10
P7	18-29	Neurophysio	1-5	7/10	4/10
P8	18-29	OT	1-5	9/10	8/10
P9	18-29	Neurology	1-5	8/10	8/10
P10	40-49	Physiotherapy	21-25	10/10	6/10
P11	40-49	Neuropsychol.	21-25	7/10	8/10
P12	30-39	OT	6-10	8/10	8/10
P13	30-39	Neurophysio.	6-10	7/10	7/10

Abbreviations: EXP, Experience; FAM, Familiarization; Tech., Technological; Neurophysio., Neurological Physiotherapy; Physio., Physiotherapy; NeuroRHB, Neurorehabilitation; OT, Occupational Therapy; Neuropsychol., Neuropsychology

Data in columns 5 and 6 are represented on a rating scale out of 10, where 10 represents the maximum value and 0 the minimum value.

Table 7.1: Characteristics of the participants.

Firstly, they were given a presentation of the objectives of this project and a demonstration of the device, in which they were able to see the operation of the device in real time and take it with their own hands. After this, an open discussion session was held in which the therapists gave their free opinion about the device, which was complemented by completing a survey. This survey aimed to know, first of all, the experience of these therapists with the use of new technologies in the clinic. But specially, to know if they found the use of this device useful and beneficial, for which patient profile they considered it most suitable, and to know their feedback regarding the ergonomics, as well as their opinion about the operation of the exercises and the associated web page, especially in terms of its complexity and convenience, in order to be able to make improvements in its development as future lines of this project.

The specific questions that were asked in the survey were the following:

- How old are you?
- What is your clinical specialty?
- How many years of experience do you have working in that specialty?
- How familiar are you with the use of devices and new technologies in the clinical setting?
- How do you feel about using devices in clinic?
- How often do you use medical devices and new technologies with patients?
- Are you satisfied with the functionality of the device?
- What level of complexity have you found in use?
- Have you met your expectations?
- Do you think it would be useful for your stroke patients?
- Would you use this device in the clinic?
- Would you recommend the use of this device to other specialists?
- Would you recommend the use of this device to patients for home use?
- For what type of patients do you think this device would be most useful and beneficial?
- What do you think of the size and weight of the device?
- What do you think of the quality of the device in terms of materials?
- What do you think of the ergonomics of the device?
- What do you think of the device evaluation form?
- What do you think of the device's training exercises?
- What do you think of the visualization of the results?
- What do you like most about using this device?
- What would you like this device to do that it doesn't?
- What limitation(s) do you find on the device?
- In your opinion, what aspects of this product could be improved?
- If you could change anything about this device, what would it be?
- Overall, what would you rate this device for use by stroke patients?

### 7.1.2 Usability study with healthy volunteers

The main objective of the usability study carried out with the healthy volunteers with whom the device was validated was to know how complex its use had been for them and whether they found it responsive to its interaction.

To this end, after the second evaluation session with the device, all participants were asked to answer a short survey. The specific questions asked were the following:

- What do you consider to be your dominant hand?
- What is your age range?
- How easy and comfortable was it to hold the device with your dominant hand?
- How easy and comfortable was it to grip the device with your NON-dominant hand?
- How complex was it for you to understand how the exercises work?
- Did the sensors on each finger seem to sensitively reflect the force you exerted?
- How difficult were the reaction speed exercises for you?
- How difficult were the memory exercises for you?
- Would you recommend its use to a family member with brain damage or alterations in hand motor function?
- Could you give us any suggestions or recommendations to improve the functionality of the device?

## 7.2 Results

### 7.2.1 Results from stroke therapists

Among the 16 participants, 13 of them answered the survey. In addition to the survey, an open discussion was held to get more ideas from the participants.

All the participants are specialized in treating stroke patients: 3 of them were neuropsychologists, 1 a neurologist, 4 occupational therapists, 4 physiotherapists, and 1 occupational therapist and physiotherapist. Most of them are quite familiar and comfortable with using devices and new technologies in the clinical setting.

They rated satisfaction with the functionality of the device with an average of 6.23 points out of a maximum of 10. They rated the complexity of using the device with an average of 4.31 out of a maximum of 10. After the explanation of the objectives of the project, the demonstration of the operation of the device met the expectations of most specialists, valuing it with a 6.07, with 10 being the highest score, exceeding expectations. 76.9% of those surveyed stated that they would use the device in the clinic and would recommend its use to other specialists, while 92.3% would also recommend its use at home.

Regarding its application in stroke patients, opinions varied significantly. On a scale where 10 signified extreme useful and 0 indicated no useful at all, the average value score was 5.46 out of 10 for those with stroke, with the most frequent rating being 7 out of 10, chosen by 5 of the 13 respondents. The lowest scores were given by the specialists who most missed the inclusion of the thumb in the device and asked ergonomic improvements.

After these questions, they were asked for what type of patients they considered the use of this device most convenient and beneficial. The responses were very diverse but are summarized below:

- Musculoskeletal pathology of the wrist-hand.
- Alzheimer disease.
- Stroke but with high functioning.
- Acquired brain damage, with high functionality / mild hemiparesis.
- Cognitive impairment, dementia.
- Patients with attention problems.
- Peripheral neuropathies.
- Trauma conditions of the hand.
- Rheumatology.

Regarding the design characteristics of the device, half of those surveyed rated its size as adequate, while the other half found it somewhat large in size. The weight and quality of the materials were suitable for all therapists. However, everyone pointed out the need to improve ergonomics to facilitate grip and wrist position.

Regarding the way of evaluating the device, everyone considered the exercises adequate. The same thing happened with the training mode exercises. Visualization of the results was simple and comfortable for all therapists.

Finally, therapists were asked to give free responses about the limitations of the device and aspects that they would improve and add.

Limitations they observed:

- Non-inclusion of the thumb.
- Position of the LEDs (difficult to see depending on the type of grip).
- Ergonomics could be improved (especially due to wrist position).
- Difficulty for the patient to start tasks when having to access a website.
- Big size.

Characteristics they would incorporate into the device:

- Sensitive feedback.
- Auditory feedback.
- More difficulty levels.

- Record grip strength of the overall hand, not just the fingers.
- That can be used without the need for a website.
- Inclusion of the thumb.
- Be able to ignore specific fingers.
- Inclusion of a strap or a base or support so that the position is fixed and the grip more stable.

Also, they were asked to indicate the aspect they liked most about the device:

- Portable.
- Home rehabilitation.
- Easy to use.
- Gamification.
- Feedback for the patient.
- Economic.
- Levels of complexity.
- Combination of motor and cognitive aspects.

In general, and only thinking about stroke patients, therapists rated the device 5.7 out of 10 as a tool for evaluating and training stroke patients.

After the final open discussion with the stroke specialists, different clinical characteristics were extracted that would fit the end user profile with Acquired Brain Injury (AIB) for the use of the AMBER device:

- **Preservation of Cognitive Abilities:** Patients should have a relatively intact visual memory to memorize and reproduce the light sequences.
- **Appropriate Fine Motor Level:** They must have mild motor impairment, which allows them to make precise movements to adjust their fingers and respond to the lights emitted by the device. Sufficient dexterity to interact with the sensors is essential to reproduce the sequences.
- **Tolerance of Lack of Thumb Support and Wrist Control:** Despite the lack of thumb support and the requirement for wrist motor control, patients with minimal involvement in these areas may adapt better to the device. Having some ability to perform pincer movements with the fingers without a specific thumb support would be beneficial.
- **Muscle Tone:** Patients with moderate or controllable muscle tone may be better suited to use the device. Although the device evaluates and strengthens the clamp force in the distal interphalangeal areas, it is essential that patients have muscle tone that allows them to interact with precision and control in these areas without presenting excessive spastic or rigid muscle tone, which could make it difficult the execution of tasks.

- **Transfer to ADL:** Although the device focuses on specific motor and cognitive training, it is essential to evaluate how these acquired skills can be transferred to everyday tasks. Patients who can generalize the skills developed with the device to ADL, such as grasping objects, performing precise movements when dressing or feeding, will have greater therapeutic benefit.

These clinical criteria would make it difficult for most of post-stroke patients to access the device. For this reason, it was suggested to also test the device in other pathologies, such as peripheral neuropathies of the upper limb, rehabilitation after fracture of the distal third of the radio-ulnar or carpus, patients with distal involvement of the upper limb due to rheumatic pathology, among others.

### 7.2.2 Results from healthy volunteers

Among the 36 participants, 23 of them answered the survey. Of all those surveyed, 90.9% found the device easy or very easy to grab while using it with their dominant hand. On the other side, with the non-dominant hand the percentage decreased to 54.5%, with 4.5% of them finding it difficult to grasp, as shown in Figure 7.1.

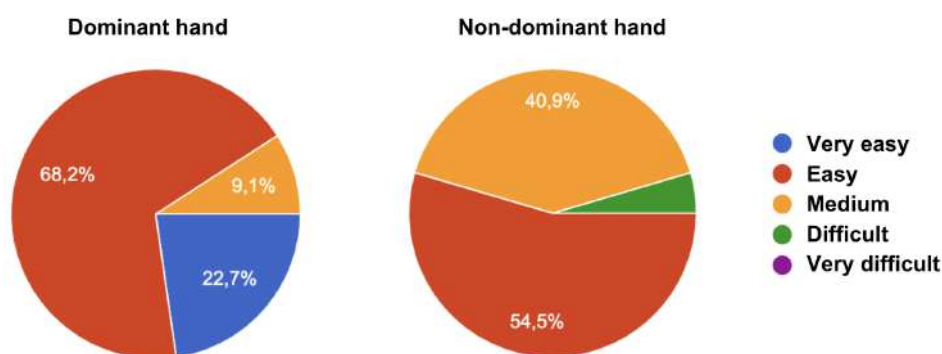


Figure 7.1: How easy it was for the volunteers to grasp the device with their dominant hand (left graph) and non-dominant hand (right graph).

Regarding understanding the functioning of the device, Figure 7.2 shows that 95.4% of the volunteers found it easy or very easy to understand how the device and its exercises work.

About the difficulty on the performance of the exercises, Figure 7.2 that 31.8% of the users did not find the reaction speed exercises (exercise 2) difficult at all, while the remaining 68.2% found them easy. And with respect to the memory exercises, 9.1% found them quite difficult, 72.7% found them somewhat difficult, and the remaining 9.1% found them easy.

Furthermore, all participants thought that the device was reasonably accurate with respect to the force they were doing, as shown in Figure 7.4.

Finally, 81.8% stated with certainty that they would recommend the use of this device to a family member with stroke, and no volunteer rejected it.

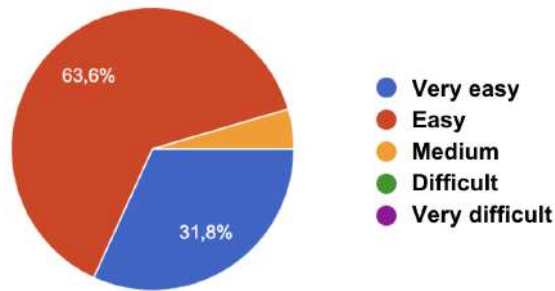


Figure 7.2: How complex it was for the volunteers to understand how the device and the exercises work.

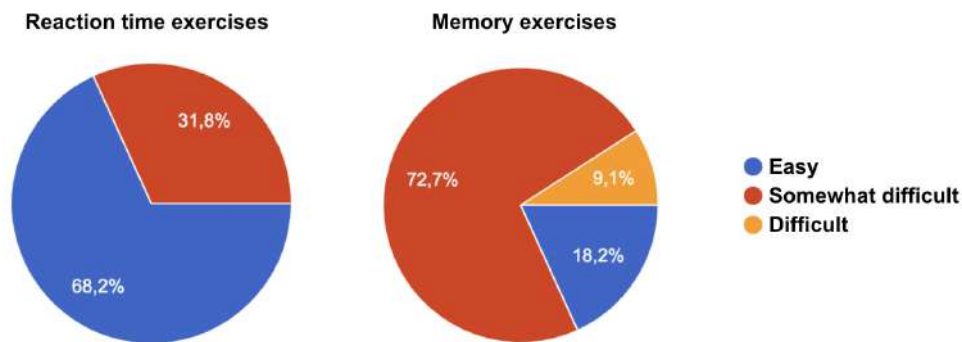


Figure 7.3: How difficult it was for the volunteers to perform the Reaction Time (graph on the left) and Memory (graph on the right) exercises.

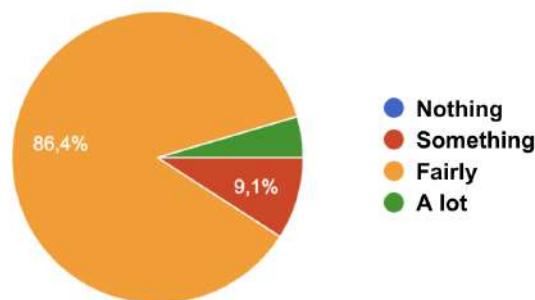


Figure 7.4: Accuracy/sensitivity perception of the device by the users.

In addition to these questions, the volunteers were asked for possible suggestions or recommendations that could improve their user experience with the device, from which the following suggestions were obtained:

- Create a position for the thumb.
- Ergonomics adjustments to improve grip comfort.
- Sound effects apart from lighting.

## 7.3 Discussion

Overall, the results suggest a positive perception of the device, although they also highlight significant areas for improvement.

The average satisfaction score with the functionality of the device, given by the therapists, was 6.23 out of 10, indicating a moderate level of acceptance. This assessment, together with the fact that 76.9% of respondents stated that they would use the device in the clinic and recommend it to other specialists, suggests a perceived usefulness of the device in the professional setting. However, the diversity of opinions regarding the inclusion of the thumb and the necessary ergonomic improvements highlight the importance of considering comfort and physical functionality in the design of rehabilitation devices.

When comparing these results with usability studies of other rehabilitation devices reported in the literature, it is observed that the inclusion of the opinion of both patients and therapists is relatively uncommon, which adds value to our study due to its holistic approach. For example, many devices focus exclusively on functionality without considering ergonomic aspects or the ultimate functionality of all fingers, which is crucial for a wide range of movements and daily tasks. The survey results also indicate that the device is considered more suitable for a wide spectrum of pathologies. Not only for post-stroke patients, but also for those with peripheral neuropathies, traumatic hand conditions, and rheumatic pathologies, among others. This diversity in potential application underscores the wide range of situations in which its use is proposed, outperforming many reviewed devices that are limited to specific conditions.

Regarding the inclusion of the thumb, feedback suggests that it is a fundamental aspect missing from our device, which is consistent with literature pointing to the importance of the thumb in performing precision and grip tasks. Comparison with existing devices shows that few effectively include the thumb in their designs, highlighting an opportunity for improvement and differentiation for our device.

To conclude, the results of the usability surveys indicate an overall positive perception of the device, with clear potential for its application in various clinical contexts. However, the areas identified for improvement, especially in terms of ergonomics and thumb inclusion, are critical to maximizing its usefulness and acceptance among end users. Comparison with other devices in the literature highlights both strengths and opportunities for improvement for our device, underscoring the importance of a design that considers both functionality and user comfort.

## 8. General discussion

The main objective of this thesis was to present a new device for hand motor and cognitive evaluation and rehabilitation, throughout its design, development, and validation. This device was designed targeting individuals with neurological impairments and specifically stroke, so it underwent a comprehensive evaluation process in line with the specified requirements, taking into consideration its intended application, human factors as handedness, and potential future clinical use.

First of all, a literature search was conducted for current technological devices used for diagnostic and therapeutic purposes of both hand and cognitive function as part of this thesis's state-of-the-art review. It was found that none of these devices are designed to train cognitive and motor functions simultaneously, reinforcing the relevance of developing and utilizing a device that integrates both dimensions. Additionally, most of today's devices do not allow for continuous data recording and storage or remote access to these data, which is essential for monitoring the status and progress of the user. The existing devices are often large, heavy, expensive, and challenging to use, limiting access for many patients. This issue is particularly important among patients living in rural areas or without rehabilitation facilities near their homes. In situations such as the recent Covid-19 pandemic, accessing a hospital for rehabilitation sessions was a significant challenge and devices like this would have been very useful.

Following an exhaustive search of the evidence concerning the impact of hand rehabilitation on cognition in stroke patients, a systematic review was conducted as part of Objective 1 of this thesis (shown in Chapter 3), "to review and quantitatively synthesize the evidence regarding the impact of hand RHB on cognition post-stroke". It revealed a significant relationship between hand motor interventions and cognitive outcomes in stroke cases, strength and robot-assisted types of training seemed to be the most effective interventions to enhance global cognition post-stroke. These results are in line with studies showing that hand grip training and grip strength are tightly related to global cognition in healthy old adults. In the case of stroke rehabilitation, grip force control may be a direct result of cognitive adaptations during task learning and reflect sensory-motor network changes. Cognitive improvements in hand rehabilitation can be expected to happen mainly on the central executive network.

The results of this systematic review highlight the importance of considering the clinical effects than hand motor interventions may have beyond purely physical aspects and underscore the importance of considering rehabilitative interventions that simultaneously address motor and cognitive aspects. These results confirm our hypothesis

that there is evidence demonstrating a correlation between hand rehabilitation and cognitive improvement in patients who have suffered a stroke.

However, some limitations were also pointed out about this Systematic Review, one of the most relevant was the limitation for quantitative synthesis of domain-specific cognitive effects due to the diversity of evaluation tools used.

Regarding participant characteristics, heterogeneous cognitive levels at baseline were found across studies, with at least some subgroups of individuals with stroke presenting mild cognitive impairment, which may impede direct translation of the results into clinical practice.

After those findings, while meeting the Objective 2 of this thesis (in Chapter 4), "design a portable device capable of gathering data from the interaction with the patient's hand through sensors and colorful light stimuli", a new device was designed with special attention to the requirements identified by an expert forum. Among the device requirements identified, it needed to be small, portable, light, economical, and easy to use, so that patients could operate it independently from home without help, as well as from the clinic with a therapist. Furthermore, the design should be simple but adaptable for different user profiles (i.e., patients with larger and smaller hands), so that a single device can be useful for all patients. The device should allow for motor and cognitive training in a motivating way for the user and ideally enable therapists to monitor patient progress remotely.

Following these desired specifications, the device was designed with an innovative focus on sensory interaction and light stimulation, thanks to different electronic components such as pressure sensors and LEDs connected to a microprocessor. Its electronic components successfully allowed the designed device to be relatively small and constructed in an affordable ergonomic structure capable of effectively capture data from the user's interaction with the device. Moreover, its adaptability and usability focus make it particularly suitable for personalized rehabilitation, crucial in the recovery of stroke patients.

However, the type of battery used was found to be susceptible of improvement, since its limited battery charge may restrict its extensive use, often necessitating connection to a power source for prolonged usage. Additionally, the absence of a specific place and sensor for the thumb (first digit) was identified as a drawback, since many daily activities heavily rely on the use of this finger, its exclusion may limit the device's full potential in interactions with users.

The tasks designed for the device as part of Objective 3 (in Chapter 5) were focused in the evaluation and training of motor and cognitive variables through the user's interaction with the device, taking full advantage of the hardware design (in Chapter 4), and aligning with the findings of Objective 1. Various exercises and levels of difficulty were designed, focusing on both motor and cognitive aspects, and two operating modes were developed to fulfill the purpose of this device: a training mode and an evaluation mode. This unique device was designed to be used both in training sessions and for the evaluation of the patient's status, so it would allow to be used in different phases of the patient's recovery thanks to its various difficulty levels. These tasks were designed

in user-friendly and gamified manner, to offer an innovative and appealing method for rehabilitation, potentially improving adherence and treatment effectiveness. However, it is important to note that the device's pre-programmed tasks may be limiting for comprehensive clinical usage. While the current programs are useful, the device would benefit from the inclusion of newer and more flexible programming options that would allow therapists to modify and customize programs according to specific needs.

Following the design and development of the device, and as part of the Objective 4 of this thesis (in Chapter 6), a validation protocol was established with a group of healthy adult volunteers to assess the technical capabilities and reliability of the device as a motor and cognitive assessment method. These subjects participated in two testing sessions on different days. On the first day, they used the AMBER device with all its different tasks and levels, as well as performed a series of motor and cognitive assessments for data comparison. On the second day, they exclusively used the AMBER device to analyze its test-retest reliability. After an in-depth analysis, the device demonstrated technical capabilities that allow for the desired assessments to be made with minimal error at a steady state. Additionally, the accuracy of its assessment mode was thoroughly tested. It can measure the precise force exerted by each finger and provide an assessment of various cognitive functions such as processing speed, attention, and memory. The Test-Retest reliability for the three measures (strength, reaction time, and memory) showed moderate to good results. The validation of the device demonstrated its reliability for assessing motor and cognitive variables from healthy subjects, confirming its potential as an assessment tool in cognitive and motor rehabilitation of stroke patients.

Finally, to meet the Objective 5 of this thesis, the usability of the device was analyzed by therapists specialized in stroke and also by the healthy volunteers which participated on the validation. After a presentation and a demonstration of the functioning of device, a group of therapists answered a survey giving their objective opinion about the device design and its operation. This survey helped us see the potential applications of the device, since practically everyone stated that they would use it in the clinic and that they would recommend its home use to many of their patients. They perceived its user-friendly interface and considered it beneficial for the rehabilitation of some profiles of stroke patients and also suggested an application on other traumatological and neurological diseases demonstrating the potential versatility of the device. However, they observed some possible improvements such as better ergonomics that may facilitate stabilization of the grip and wrist position. Another valuable suggestion was to transform the pre-programmed static tasks, into a more flexible programmable platform which could control the sequences of the tasks or at least have a wider range of tasks that allow more variability in the exercises, and therefore allow greater adaptability for more patient profiles. In this way, their feedback also served to create new future lines of research in this project, which would help improve the functionality of the device and reach greater user profiles. On the other hand, the feedback from the volunteers was also very useful, pointing out that there are possible improvements in ergonomics but they were very satisfied with the operability, gamification and difficulty of the exercises was appropriate as a first prototype.

In summary, the novel design and dual-functionality of this device for cognitive and

physical assessment and rehabilitation were considered to be eligible for patenting. Positive preliminary feedback and an international patent request underlines that further design improvements and iterative refinements are feasible. This process will hopefully culminate in its commercial availability for clinical use and the opportunity to conduct a clinical trial to evaluate its effects on patients recovering from stroke

Finally, it is worth highlighting as part of this general discussion, the contribution that the international stay of this doctorate had in the thesis. Participation in similar projects within the Neuromechanical Modeling and Engineering Lab of the University of Twente allowed us to learn about other studies and development of devices within the area of neurorehabilitation. This, first of all, allowed the knowledge of different approach methods for the design and prototyping of medical devices, usability studies with healthy volunteers, and also data analysis techniques used in this project. Furthermore, it allowed us to develop ideas for future lines in terms of programming and data processing that would not have been imagined without this international stay.

## 9. Limitations and future lines

During the development of this project, some limitations of the device were identified. From each of those limitations, new ideas for improvement arose as future lines of research on this project. Both limitations with each solution are listed below:

- **Battery capacity:** even the battery used was selected for its small size and easy connection to the microprocessor, the limited battery charge may restrict its extensive use, often necessitating connection to a power source for prolonged usage. To solve this, the change the battery for one with more capacity is proposed. Even the battery used was selected for its small size and easy connection to the microprocessor, the limited battery charge may restrict its extensive use, often necessitating connection to a power source for prolonged usage.
- **Absence of a place for the thumb:** the absence of a specific place and sensor for the thumb (first digit) may limit the device's full potential in interactions with users, since many daily activities heavily rely on the use of this finger. As a future line, it is proposed to design a new prototype that includes a place and sensor for the thumb.
- **Hand and wrist stability:** since the device does not have a support base for a surface, or a strap that allows it to be attached at all times to the patient's hand or wrist, this can cause instability in patients with a more severe degree of motor impairment, such as in cases of dystonia or reduced abduction capabilities. In this case, a new design will also include a strap or similar so that the user has the device attached to his wrist and therefore if the patient lets it go or it slips, it does not fall.
- **Static pre-programmed tasks:** there is no possibility of modifying the exercises by the therapists. To address this, the pre-programmed sequences of the exercises will be randomized and more levels of difficulty will be developed for each type of exercise. In addition, the exercises could be programmed in a way that the therapist can easily modified them through the web, so that they can adapt the exercises according to the needs of each patient.

Following the integration of the identified enhancements, the device will be prepared for submission for medical device prototype certification. Additionally, it will be ready to commence a clinical trial with stroke patients to assess AMBER's efficacy as an instrument for cognitive and motor rehabilitation.

Additionally, it is important to highlight that this device has great potential to apply

Machine Learning and automatic learning techniques directly in the device. Using this advanced analysis, the device will be able to compare in real time the execution of the exercises of a patient with a desirable pattern that can be previously established, so that the device can indicate to the therapist the degree of similarity with said desired pattern. Also through classification models, the device could learn from each patient's data and in this way could help tutor the patient's training progression in real time, for example indicating whether or not a certain exercise should be repeated, avoiding unnecessary repetitions and improving the effectiveness of the therapy, focusing only on the tasks that the patient should improve.

# 10. Conclusions

Below, the main conclusions derived from this study are recapitulated:

- There is evidence that hand motor interventions can improve global cognition in people with stroke and possibly focusing on frontoexecutive functions (H1).
- The combination of strength training or robot-assisted training and conventional RHB may be the most effective intervention to improve global cognition according to the MMSE (H1).
- A Portable, cheap and easy to use device would fill unmet needs in hand neurorehabilitation devices ecosystem (H2).
- A small, light and simple design device would constitute a useful tool to use in rehabilitation at the clinic as well as home (H2).
- The adaptability of the device to different hand sizes is a valuable feature making it usable by a greater number of patients (H2).
- The electronic components integrated in AMBER are efficient capturing the interaction with the subjects (H2).
- The user-friendly interface and gamification of tasks of AMBER makes its use more appealing to patients (H3).
- The cognitive evaluation through the interaction with the hand and fingers is possible using AMBER device (H3).
- Motor evaluation through the interaction with the hand and fingers is possible using AMBER device (H3).
- AMBER device has shown a good test-retest reliability, obtaining motor and cognitive variables from the user (H4).
- The programmed tasks on AMBER make it possible to train and evaluate both motor functions of the hand and cognitive abilities simultaneously (H4).
- Therapists value positively the design and functionality of the device (H5).
- Healthy volunteer users indicated that the use of the device and the exercises were simple and intuitive highlighting its potential as a reliable and versatile tool (H5).

# 11. Scientific contributions

## 11.1 Patent

Application Number and Date: 300470544, December 21, 2022.

Publication Number: EP22383249.4.

Inventors: Juan Pablo Romero, Roberto Álvarez Fernández, Laura Valenzuela López, Rodrigo Martínez, Gabriel Alfonso Delgado Oleas.

## 11.2 Scientific Papers

1. "Effects of Hand Motor Interventions on Cognition Post-Stroke: A Systematic Review and Bayesian Network Meta-Analysis." *Archives of Physical and Rehabilitation Medicine* (WOS-JCR-Q1, Impact Factor: 4.3, Quartile: Q1). Published. DOI: <https://doi.org/10.1016/j.apmr.2023.12.013>.
2. "AMBER: A Device for Hand Motor and Cognitive Rehabilitation. Development and Proof of Concept." *IEEE Transactions on Neural Systems and Rehabilitation Engineering* (WOS-JCR-Q1, Impact Factor: 4.9, Quartile: Q1). Published. DOI: <https://doi.org/10.1109/TNSRE.2024.3429155>

## 11.3 Conference Contributions

Title of the work: "AMBER: a device for hand motor and cognitive rehabilitation. Development and proof of concept".

Name of the conference: 13th World Congress for NeuroRehabilitation Event  
type: Congress

Geographical scope: International, non-EU

Type of participation: Participatory - Poster

Review before acceptance: Yes

Corresponding author: No

City of the event: Canada

Start date: 22/05/2024

End date: 25/05/2024

Organizing entity: World Federation of NeuroRehabilitation (WFNR)

## 11.4 Scientific Recognition

The AMBER project has been selected for the Healthstart Madrid 2024 call (<https://www.madrimasd.org/healthstart/>) to promote the creation of technological start-ups in the health sector, coming from hospitals, health centres, research centres, universities and independent entrepreneurs, exclusively from the Community of Madrid.

# Appendix

## Appendix A: Supplementary information from the Systematic Review

Concept	Search strategy number	Search terms and boolean operators
Stroke	S1	((stroke OR poststroke OR post-stroke OR “cerebrovascular disorder” OR “cerebrovascular accident” OR “cerebrovascular disease” OR “brain damage” OR “brain injury”) OR (ischemia OR ischaemia OR “brain ischemia” OR “brain ischaemia” OR “ischemic attack”) OR (haemorrhage OR hemorrhage OR haematoma OR hematoma))
Hand rehabilitation interventions and hand motor variables	S2	((“hand rehabilitation” OR “hand therapy” OR “hand intervention” OR “hand recovery” OR “hand training” OR “hand program” OR “hand approach”) OR (“hand function” OR “hand motor skill” OR “hand motor ability” OR “fine motor skill”) OR (“hand strength” OR “grip strength” OR “pinch strength” OR “pinch force” OR “finger strength”) OR (“hand dexterity” OR “manual dexterity” OR “finger dexterity”))
Cognition and general cognitive function	S3	(cognition OR “cognitive level” OR “cognitive function” OR “cognitive ability” OR “cognitive impairment” OR “cognitive disorder” OR “cognitive deficit” OR “cognitive dysfunction” OR “cognitive disfunction” OR “neuropsychology” OR “neuropsychological”)
Attention and neglect	S4	((“divided attention” OR “focused attention” OR “selective attention” OR “sustained attention” OR “visual attention” OR “attention span” OR “attentional span” OR arousal OR vigilance) OR (neglect OR “hemineglect” OR “hemi-neglect” OR “unilateral neglect” OR “spatial neglect” OR inattention))
Memory	S5	(“explicit memory” OR “implicit memory” OR “long term memory” OR “short term memory” OR “working memory” OR “procedural memory” OR “episodic memory”)
Executive functions and praxis	S6	((“executive function” OR “executive dysfunction” OR “dysexecutive syndrome” OR “set shifting” OR “switching” OR “monitoring” OR “interference control”) OR (apraxia OR “motor apraxia” OR “limb apraxia”))
Perception	S7	(perception OR “perceptual disorder” OR “visual perception” OR agnosia OR prosopagnosia OR stereognosis)

Table 11.1: Search strategies based on the key concepts identified for the review. MeSH terms were searched on each search engine wherever possible.

The search strategies S1 and S2 composed the common search command as (S1 AND S2). On each database, the search strategies S3-S7 were added to this common search command as (S1 AND S2 AND S3, S1 AND S2 AND S4, etc).

Database	Number of records retrieved (S1 AND S2 AND ...)						Subtotal	After duplicate removal	Total	After duplicate removal
	S3	S4	S5	S6	S7					
<b>PubMed</b>	717	133	48	243	42	1183	990			
<b>Cochrane CENTRAL</b>	238	30	14	96	55	433	329			
<b>Web of Science</b>	396	80	26	202	195	899	745	3415	2271	
<b>Scopus</b>	623	91	53	308	43	1118	940			
<b>CINAHL</b>	305	39	8	78	75	505	411			
<b>Embase</b>	203	53	19	102	25	402	344			

Table 11.2: Initial results retrieved per search engine and per each combination of search strategies.

The following tables show the search strings for each database, including PubMed, Cochrane Library, Web of Science, Scopus, CINAHL, and Embase. The common strategy included the concepts of stroke, hand motor interventions, and hand motor function variables. The specific strategies included the concepts of general cognition (S3), attention (S4), memory (S5), executive functioning and praxis (S6), and perception (S7).

<b>PubMed (MEDLINE)</b>	
<b>S3</b>	(((stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury") OR (ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack") OR (haemorrhage OR hemorrhage OR haematoma OR hematoma))) AND (((("hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach") OR ("hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill") OR ("hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength") OR ("hand dexterity" OR "manual dexterity" OR "finger dexterity")))) AND ((cognition OR "cognitive level" OR "cognitive function" OR "cognitive ability" OR "cognitive impairment" OR "cognitive disorder" OR "cognitive deficit" OR "cognitive dysfunction" OR "cognitive disfunction" OR "neuropsychology" OR "neuropsychological")))
<b>S4</b>	(((stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury") OR (ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack") OR (haemorrhage OR hemorrhage OR haematoma OR hematoma))) AND (((("hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach") OR ("hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill") OR ("hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength") OR ("hand dexterity" OR "manual dexterity" OR "finger dexterity")))) AND (((("divided attention" OR "focused attention" OR "selective attention" OR "sustained attention" OR "visual attention" OR "attention span" OR "attentional span" OR arousal OR vigilance) OR (neglect OR "hemineglect" OR "hemi-neglect" OR "unilateral neglect" OR "spatial neglect" OR inattention)))
<b>S5</b>	(((stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury") OR (ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack") OR (haemorrhage OR hemorrhage OR haematoma OR hematoma))) AND (((("hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach") OR ("hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill") OR ("hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength") OR ("hand dexterity" OR "manual dexterity" OR "finger dexterity")))) AND ((("explicit memory" OR "implicit memory" OR "long term memory" OR "short term memory" OR "working memory" OR "procedural memory" OR "episodic memory")))
<b>S6</b>	(((stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury") OR (ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack") OR (haemorrhage OR hemorrhage OR haematoma OR hematoma))) AND (((("hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach") OR ("hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill") OR ("hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength") OR ("hand dexterity" OR "manual dexterity" OR "finger dexterity")))) AND (((("executive function" OR "executive dysfunction" OR "dysexecutive syndrome" OR "set shifting" OR "switching" OR "monitoring" OR "interference control") OR (apraxia OR "motor apraxia" OR "limb apraxia")))
<b>S7</b>	(((stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury") OR (ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack") OR (haemorrhage OR hemorrhage OR haematoma OR hematoma))) AND (((("hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach") OR ("hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill") OR ("hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength") OR ("hand dexterity" OR "manual dexterity" OR "finger dexterity")))) AND ((perception OR "perceptual disorder" OR "visual perception" OR agnosia OR prosopagnosia OR stereognosis))

Table 11.3: Search strings for PubMed database.

<b>Cochrane (CENTRAL)</b>	
<b>S3</b>	((stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury") OR (ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack") OR (haemorrhage OR hemorrhage OR haematoma OR hematoma)):ti,ab,kw AND (((("hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach") OR ("hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill") OR ("hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength") OR ("hand dexterity" OR "manual dexterity" OR "finger dexterity"))):ti,ab,kw AND ((cognition OR "cognitive level" OR "cognitive function" OR "cognitive ability" OR "cognitive impairment" OR "cognitive disorder" OR "cognitive deficit" OR "cognitive dysfunction" OR "cognitive disfunction" OR "neuropsychology" OR "neuropsychological")):ti,ab,kw
<b>S4</b>	((stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury") OR (ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack") OR (haemorrhage OR hemorrhage OR haematoma OR hematoma)):ti,ab,kw AND (((("hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach") OR ("hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill") OR ("hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength") OR ("hand dexterity" OR "manual dexterity" OR "finger dexterity"))):ti,ab,kw AND (((("divided attention" OR "focused attention" OR "selective attention" OR "sustained attention" OR "visual attention" OR "attention span" OR "attentional span" OR arousal OR vigilance) OR (neglect OR "hemineglect" OR "hemi-neglect" OR "unilateral neglect" OR "spatial neglect" OR inattention)):ti,ab,kw
<b>S5</b>	((stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury") OR (ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack") OR (haemorrhage OR hemorrhage OR haematoma OR hematoma)):ti,ab,kw AND (((("hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach") OR ("hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill") OR ("hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength") OR ("hand dexterity" OR "manual dexterity" OR "finger dexterity"))):ti,ab,kw AND (("explicit memory" OR "implicit memory" OR "long term memory" OR "short term memory" OR "working memory" OR "procedural memory" OR "episodic memory")):ti,ab,kw
<b>S6</b>	((stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury") OR (ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack") OR (haemorrhage OR hemorrhage OR haematoma OR hematoma)):ti,ab,kw AND (((("hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach") OR ("hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill") OR ("hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength") OR ("hand dexterity" OR "manual dexterity" OR "finger dexterity"))):ti,ab,kw AND (((("executive function" OR "executive dysfunction" OR "dysexecutive syndrome" OR "set shifting" OR "switching" OR "monitoring" OR "interference control") OR (apraxia OR "motor apraxia" OR "limb apraxia"))):ti,ab,kw
<b>S7</b>	((stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury") OR (ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack") OR (haemorrhage OR hemorrhage OR haematoma OR hematoma)):ti,ab,kw AND (((("hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach") OR ("hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill") OR ("hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength") OR ("hand dexterity" OR "manual dexterity" OR "finger dexterity"))):ti,ab,kw AND ((perception OR "perceptual disorder" OR "visual perception" OR agnosia OR prosopagnosia OR stereognosis)):ti,ab,kw

Table 11.4: Search strings for Cochrane Library database.

<b>Web of Science</b>	
<b>S3</b>	((stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury") OR (ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack") OR (haemorrhage OR hemorrhage OR haematoma OR hematoma)) (Topic) and (((hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach") OR ("hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill") OR ("hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength") OR ("hand dexterity" OR "manual dexterity" OR "finger dexterity")) (Topic) and (cognition OR "cognitive level" OR "cognitive function" OR "cognitive ability" OR "cognitive impairment" OR "cognitive disorder" OR "cognitive deficit" OR "cognitive dysfunction" OR "cognitive disfunction" OR "neuropsychology" OR "neuropsychological") (Topic)
<b>S4</b>	((TS=((stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury") OR (ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack") OR (haemorrhage OR hemorrhage OR haematoma OR hematoma)))) AND TS=((("hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach") OR ("hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill") OR ("hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength") OR ("hand dexterity" OR "manual dexterity" OR "finger dexterity")))) AND TS=((("divided attention" OR "focused attention" OR "selective attention" OR "sustained attention" OR "visual attention" OR "attention span" OR "attentional span" OR arousal OR vigilance) OR (neglect OR "hemineglect" OR "hemi-neglect" OR "unilateral neglect" OR "spatial neglect" OR inattention)))
<b>S5</b>	((TS=((stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury") OR (ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack") OR (haemorrhage OR hemorrhage OR haematoma OR hematoma)))) AND TS=((("hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach") OR ("hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill") OR ("hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength") OR ("hand dexterity" OR "manual dexterity" OR "finger dexterity")))) AND TS=((("explicit memory" OR "implicit memory" OR "long term memory" OR "short term memory" OR "working memory" OR "procedural memory" OR "episodic memory")))
<b>S6</b>	((TS=((stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury") OR (ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack") OR (haemorrhage OR hemorrhage OR haematoma OR hematoma)))) AND TS=((("hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach") OR ("hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill") OR ("hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength") OR ("hand dexterity" OR "manual dexterity" OR "finger dexterity")))) AND TS=((("executive function" OR "executive dysfunction" OR "dysexecutive syndrome" OR "set shifting" OR "switching" OR "monitoring" OR "interference control") OR (apraxia OR "motor apraxia" OR "limb apraxia")))
<b>S7</b>	((TS=((stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury") OR (ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack") OR (haemorrhage OR hemorrhage OR haematoma OR hematoma)))) AND TS=((("hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach") OR ("hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill") OR ("hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength") OR ("hand dexterity" OR "manual dexterity" OR "finger dexterity")))) AND TS=((perception OR "perceptual disorder" "visual perception" OR agnosia OR prosopagnosia OR stereognostic))

Table 11.5: Search strings for Web of Science database.

<b>Scopus</b>	
<b>S3</b>	( TITLE-ABS-KEY ( ( ( stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury" ) OR ( ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack" ) OR ( haemorrhage OR hemorrhage OR haematoma OR hematoma ) ) ) AND TITLE-ABS-KEY ( ( ( "hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach" ) OR ( "hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill" ) OR ( "hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength" ) OR ( "hand dexterity" OR "manual dexterity" OR "finger dexterity" ) ) ) ) AND TITLE-ABS-KEY ( ( cognition OR "cognitive level" OR "cognitive function" OR "cognitive ability" OR "cognitive impairment" OR "cognitive disorder" OR "cognitive deficit" OR "cognitive dysfunction" OR "cognitive disfunction" OR "neuropsychology" OR "neuropsychological" ) ) )
<b>S4</b>	( TITLE-ABS-KEY ( ( ( stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury" ) OR ( ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack" ) OR ( haemorrhage OR hemorrhage OR haematoma OR hematoma ) ) ) AND TITLE-ABS-KEY ( ( ( "hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach" ) OR ( "hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill" ) OR ( "hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength" ) OR ( "hand dexterity" OR "manual dexterity" OR "finger dexterity" ) ) ) ) AND TITLE-ABS-KEY ( ( ( "divided attention" OR "focused attention" OR "selective attention" OR "sustained attention" OR "visual attention" OR "attention span" OR "attentional span" OR arousal OR vigilance ) OR ( neglect OR "hemineglect" OR "hemi-neglect" OR "unilateral neglect" OR "spatial neglect" OR inattention ) ) ) )
<b>S5</b>	( TITLE-ABS-KEY ( ( ( stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury" ) OR ( ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack" ) OR ( haemorrhage OR hemorrhage OR haematoma OR hematoma ) ) ) AND TITLE-ABS-KEY ( ( ( "hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach" ) OR ( "hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill" ) OR ( "hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength" ) OR ( "hand dexterity" OR "manual dexterity" OR "finger dexterity" ) ) ) ) AND TITLE-ABS-KEY ( ( ( "explicit memory" OR "implicit memory" OR "long term memory" OR "short term memory" OR "working memory" OR "procedural memory" OR "episodic memory" ) ) ) )
<b>S6</b>	( TITLE-ABS-KEY ( ( ( stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury" ) OR ( ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack" ) OR ( haemorrhage OR hemorrhage OR haematoma OR hematoma ) ) ) AND TITLE-ABS-KEY ( ( ( "hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach" ) OR ( "hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill" ) OR ( "hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength" ) OR ( "hand dexterity" OR "manual dexterity" OR "finger dexterity" ) ) ) ) AND TITLE-ABS-KEY ( ( ( "executive function" OR "executive dysfunction" OR "dysexecutive syndrome" OR "set shifting" OR "switching" OR "monitoring" OR "interference control" ) OR ( apraxia OR "motor apraxia" OR "limb apraxia" ) ) ) )
<b>S7</b>	( TITLE-ABS-KEY ( ( ( stroke OR outstroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury" ) OR ( ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack" ) OR ( haemorrhage OR hemorrhage OR haematoma OR hematoma ) ) ) AND TITLE-ABS-KEY ( ( ( "hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach" ) OR ( "hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill" ) OR ( "hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength" ) OR ( "hand dexterity" OR "manual dexterity" OR "finger dexterity" ) ) ) ) AND TITLE-ABS-KEY ( ( perception OR "perceptual disorder" OR "visual perception" OR agnosia OR prosopagnosia OR stereognosis ) ) )

Table 11.6: Search strings for Scopus database.

<b>CINAHL (via EBSCO)</b>	
<b>S3</b>	( (stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury") OR (ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack") OR (haemorrhage OR hemorrhage OR haematoma OR hematoma) ) AND ( ("hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach") OR ("hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill") OR ("hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength") OR ("hand dexterity" OR "manual dexterity" OR "finger dexterity")) ) AND ( (cognition OR "cognitive level" OR "cognitive function" OR "cognitive ability" OR "cognitive impairment" OR "cognitive disorder" OR "cognitive deficit" OR "cognitive dysfunction" OR "cognitive disfunction" OR "neuropsychology" OR "neuropsychological") ) )
<b>S4</b>	( (stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury") OR (ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack") OR (haemorrhage OR hemorrhage OR haematoma OR hematoma) ) AND ( ("hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach") OR ("hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill") OR ("hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength") OR ("hand dexterity" OR "manual dexterity" OR "finger dexterity")) ) AND ( ("divided attention" OR "focused attention" OR "selective attention" OR "sustained attention" OR "visual attention" OR "attention span" OR "attentional span" OR arousal OR vigilance) OR (neglect OR "hemineglect" OR "hemi-neglect" OR "unilateral neglect" OR "spatial neglect" OR inattention)) )
<b>S5</b>	( (stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury") OR (ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack") OR (haemorrhage OR hemorrhage OR haematoma OR hematoma) ) AND ( ("hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach") OR ("hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill") OR ("hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength") OR ("hand dexterity" OR "manual dexterity" OR "finger dexterity")) ) AND ( "explicit memory" OR "implicit memory" OR "long term memory" OR "short term memory" OR "working memory" OR "procedural memory" OR "episodic memory" ) )
<b>S6</b>	( (stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury") OR (ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack") OR (haemorrhage OR hemorrhage OR haematoma OR hematoma) ) AND ( ("hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach") OR ("hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill") OR ("hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength") OR ("hand dexterity" OR "manual dexterity" OR "finger dexterity")) ) AND ( ("executive function" OR "executive dysfunction" OR "dysexecutive syndrome" OR "set shifting" OR "switching" OR "monitoring" OR "interference control") OR (apraxia OR "motor apraxia" OR "limb apraxia")) )
<b>S7</b>	( (stroke OR poststroke OR post-stroke OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "brain damage" OR "brain injury") OR (ischemia OR ischaemia OR "brain ischemia" OR "brain ischaemia" OR "ischemic attack") OR (haemorrhage OR hemorrhage OR haematoma OR hematoma) ) AND ( ("hand rehabilitation" OR "hand therapy" OR "hand intervention" OR "hand recovery" OR "hand training" OR "hand program" OR "hand approach") OR ("hand function" OR "hand motor skill" OR "hand motor ability" OR "fine motor skill") OR ("hand strength" OR "grip strength" OR "pinch strength" OR "pinch force" OR "finger strength") OR ("hand dexterity" OR "manual dexterity" OR "finger dexterity")) ) AND ( perception OR "perceptual disorder" OR "visual perception" OR agnosia OR prosopagnosia OR stereognosis ) )

Table 11.7: Search strings for CINAHL database.

<b>Embase</b>	
<b>53</b>	(stroke:ti,ab,kw OR poststroke:ti,ab,kw OR 'post stroke':ti,ab,kw OR 'cerebrovascular disorder':ti,ab,kw OR 'cerebrovascular accident':ti,ab,kw OR 'cerebrovascular disease':ti,ab,kw OR 'brain damage':ti,ab,kw OR 'brain injury':ti,ab,kw OR ischemia:ti,ab,kw OR ischaemia:ti,ab,kw OR 'brain ischemia':ti,ab,kw OR 'brain ischaemia':ti,ab,kw OR 'ischemic attack':ti,ab,kw OR haemorrhage:ti,ab,kw OR hemorrhage:ti,ab,kw OR haematoma:ti,ab,kw OR hematoma:ti,ab,kw) AND ('hand rehabilitation':ti,ab,kw OR 'hand therapy':ti,ab,kw OR 'hand intervention':ti,ab,kw OR 'hand recovery':ti,ab,kw OR 'hand training':ti,ab,kw OR 'hand program':ti,ab,kw OR 'hand approach':ti,ab,kw OR 'hand function':ti,ab,kw OR 'hand motor skill':ti,ab,kw OR 'hand motor ability':ti,ab,kw OR 'fine motor skill':ti,ab,kw OR 'hand strength':ti,ab,kw OR 'grip strength':ti,ab,kw OR 'pinch strength':ti,ab,kw OR 'pinch force':ti,ab,kw OR 'finger strength':ti,ab,kw OR 'hand dexterity':ti,ab,kw OR 'manual dexterity':ti,ab,kw OR 'finger dexterity':ti,ab,kw) AND (cognition:ti,ab,kw OR 'cognitive level':ti,ab,kw OR 'cognitive function':ti,ab,kw OR 'cognitive ability':ti,ab,kw OR 'cognitive impairment':ti,ab,kw OR 'cognitive disorder':ti,ab,kw OR 'cognitive deficit':ti,ab,kw OR 'cognitive dysfunction':ti,ab,kw OR 'cognitive disfunction':ti,ab,kw OR 'neuropsychology':ti,ab,kw OR 'neuropsychological':ti,ab,kw)
<b>54</b>	(stroke:ti,ab,kw OR poststroke:ti,ab,kw OR 'post stroke':ti,ab,kw OR 'cerebrovascular disorder':ti,ab,kw OR 'cerebrovascular accident':ti,ab,kw OR 'cerebrovascular disease':ti,ab,kw OR 'brain damage':ti,ab,kw OR 'brain injury':ti,ab,kw OR ischemia:ti,ab,kw OR ischaemia:ti,ab,kw OR 'brain ischemia':ti,ab,kw OR 'brain ischaemia':ti,ab,kw OR 'ischemic attack':ti,ab,kw OR haemorrhage:ti,ab,kw OR hemorrhage:ti,ab,kw OR haematoma:ti,ab,kw OR hematoma:ti,ab,kw) AND ('hand rehabilitation':ti,ab,kw OR 'hand therapy':ti,ab,kw OR 'hand intervention':ti,ab,kw OR 'hand recovery':ti,ab,kw OR 'hand training':ti,ab,kw OR 'hand program':ti,ab,kw OR 'hand approach':ti,ab,kw OR 'hand function':ti,ab,kw OR 'hand motor skill':ti,ab,kw OR 'hand motor ability':ti,ab,kw OR 'fine motor skill':ti,ab,kw OR 'hand strength':ti,ab,kw OR 'grip strength':ti,ab,kw OR 'pinch strength':ti,ab,kw OR 'pinch force':ti,ab,kw OR 'finger strength':ti,ab,kw OR 'hand dexterity':ti,ab,kw OR 'manual dexterity':ti,ab,kw OR 'finger dexterity':ti,ab,kw) AND ('divided attention':ti,ab,kw OR 'focused attention':ti,ab,kw OR 'selective attention':ti,ab,kw OR 'sustained attention':ti,ab,kw OR 'visual attention':ti,ab,kw OR 'attention span':ti,ab,kw OR 'attentional span':ti,ab,kw OR 'arousal':ti,ab,kw OR 'vigilance':ti,ab,kw OR 'neglect':ti,ab,kw OR 'hemineglect':ti,ab,kw OR 'hemi-neglect':ti,ab,kw OR 'unilateral neglect':ti,ab,kw OR 'spatial neglect':ti,ab,kw OR 'inattention':ti,ab,kw)
<b>55</b>	(stroke:ti,ab,kw OR poststroke:ti,ab,kw OR 'post stroke':ti,ab,kw OR 'cerebrovascular disorder':ti,ab,kw OR 'cerebrovascular accident':ti,ab,kw OR 'cerebrovascular disease':ti,ab,kw OR 'brain damage':ti,ab,kw OR 'brain injury':ti,ab,kw OR ischemia:ti,ab,kw OR ischaemia:ti,ab,kw OR 'brain ischemia':ti,ab,kw OR 'brain ischaemia':ti,ab,kw OR 'ischemic attack':ti,ab,kw OR haemorrhage:ti,ab,kw OR hemorrhage:ti,ab,kw OR haematoma:ti,ab,kw OR hematoma:ti,ab,kw) AND ('hand rehabilitation':ti,ab,kw OR 'hand therapy':ti,ab,kw OR 'hand intervention':ti,ab,kw OR 'hand recovery':ti,ab,kw OR 'hand training':ti,ab,kw OR 'hand program':ti,ab,kw OR 'hand approach':ti,ab,kw OR 'hand function':ti,ab,kw OR 'hand motor skill':ti,ab,kw OR 'hand motor ability':ti,ab,kw OR 'fine motor skill':ti,ab,kw OR 'hand strength':ti,ab,kw OR 'grip strength':ti,ab,kw OR 'pinch strength':ti,ab,kw OR 'pinch force':ti,ab,kw OR 'finger strength':ti,ab,kw OR 'hand dexterity':ti,ab,kw OR 'manual dexterity':ti,ab,kw OR 'finger dexterity':ti,ab,kw) AND ('explicit memory':ti,ab,kw OR 'implicit memory':ti,ab,kw OR 'long term memory':ti,ab,kw OR 'short term memory':ti,ab,kw OR 'working memory':ti,ab,kw OR 'procedural memory':ti,ab,kw OR 'episodic memory':ti,ab,kw)
<b>56</b>	(stroke:ti,ab,kw OR poststroke:ti,ab,kw OR 'post stroke':ti,ab,kw OR 'cerebrovascular disorder':ti,ab,kw OR 'cerebrovascular accident':ti,ab,kw OR 'cerebrovascular disease':ti,ab,kw OR 'brain damage':ti,ab,kw OR 'brain injury':ti,ab,kw OR ischemia:ti,ab,kw OR ischaemia:ti,ab,kw OR 'brain ischemia':ti,ab,kw OR 'brain ischaemia':ti,ab,kw OR 'ischemic attack':ti,ab,kw OR haemorrhage:ti,ab,kw OR hemorrhage:ti,ab,kw OR haematoma:ti,ab,kw OR hematoma:ti,ab,kw) AND ('hand rehabilitation':ti,ab,kw OR 'hand therapy':ti,ab,kw OR 'hand intervention':ti,ab,kw OR 'hand recovery':ti,ab,kw OR 'hand training':ti,ab,kw OR 'hand program':ti,ab,kw OR 'hand approach':ti,ab,kw OR 'hand function':ti,ab,kw OR 'hand motor skill':ti,ab,kw OR 'hand motor ability':ti,ab,kw OR 'fine motor skill':ti,ab,kw OR 'hand strength':ti,ab,kw OR 'grip strength':ti,ab,kw OR 'pinch strength':ti,ab,kw OR 'pinch force':ti,ab,kw OR 'finger strength':ti,ab,kw OR 'hand dexterity':ti,ab,kw OR 'manual dexterity':ti,ab,kw OR 'finger dexterity':ti,ab,kw) AND ('executive function':ti,ab,kw OR 'executive dysfunction':ti,ab,kw OR 'dysexecutive syndrome':ti,ab,kw OR 'set shifting':ti,ab,kw OR 'switching':ti,ab,kw OR 'monitoring':ti,ab,kw OR 'interference control':ti,ab,kw OR 'apraxia':ti,ab,kw OR 'motor apraxia':ti,ab,kw OR 'limb apraxia':ti,ab,kw)
<b>57</b>	(stroke:ti,ab,kw OR poststroke:ti,ab,kw OR 'post stroke':ti,ab,kw OR 'cerebrovascular disorder':ti,ab,kw OR 'cerebrovascular accident':ti,ab,kw OR 'cerebrovascular disease':ti,ab,kw OR 'brain damage':ti,ab,kw OR 'brain injury':ti,ab,kw OR ischemia:ti,ab,kw OR ischaemia:ti,ab,kw OR 'brain ischemia':ti,ab,kw OR 'brain ischaemia':ti,ab,kw OR 'ischemic attack':ti,ab,kw OR haemorrhage:ti,ab,kw OR hemorrhage:ti,ab,kw OR haematoma:ti,ab,kw OR hematoma:ti,ab,kw) AND ('hand rehabilitation':ti,ab,kw OR 'hand therapy':ti,ab,kw OR 'hand intervention':ti,ab,kw OR 'hand recovery':ti,ab,kw OR 'hand training':ti,ab,kw OR 'hand program':ti,ab,kw OR 'hand approach':ti,ab,kw OR 'hand function':ti,ab,kw OR 'hand motor skill':ti,ab,kw OR 'hand motor ability':ti,ab,kw OR 'fine motor skill':ti,ab,kw OR 'hand strength':ti,ab,kw OR 'grip strength':ti,ab,kw OR 'pinch strength':ti,ab,kw OR 'pinch force':ti,ab,kw OR 'finger strength':ti,ab,kw OR 'hand dexterity':ti,ab,kw OR 'manual dexterity':ti,ab,kw OR 'finger dexterity':ti,ab,kw) AND ((perception:ti,ab,kw OR 'perceptual disorder':ti,ab,kw) AND 'visual perception':ti,ab,kw OR 'agnosia':ti,ab,kw OR 'prosopagnosia':ti,ab,kw OR 'stereognosis':ti,ab,kw)

Table 11.8: Search strings for Embase database.

## Methods

In each NMA, the selection of a random or fixed effects model was evaluated, as well as the presence of inconsistency, by analyzing the leverage graph (defined as posterior mean residual deviance of each study arm minus the deviance at the posterior mean of the fitted values) versus Bayesian residual deviance ( $w$ ) defined as each study arm contribution to the posterior mean deviance of the model. Likewise, deviance was evaluated specifically with the mean of the residual deviance ( $D_{res}$ ), effective number of parameters or sum of leverages ( $pD$ ) and Deviance Information Criteria (DIC) defined as the sum of  $D_{res}$  and  $pD$ . In these statistics, the lower the value, the better fit of the model.

In the case that a variable presented enough comparisons, the presence of inconsistency was also evaluated using the node-split method, which allows detecting the presence of significant differences between direct and indirect comparisons. In addition, if discrepancies in the plot of posterior mean of consistency vs. inconsistency models were detected, an additional meta regression model was applied adding as covariables age and baseline scores.

The convergence of the posterior distributions of the parameters through Markov Chain Monte Carlo sampling was evaluated with the trace plot of mean of each comparison over all the iterations, as well as with the density plot of the subsequent effect size estimate.



Figure 11.1: Structure of the networks for Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE). The size of the nodes and thickness of the comparisons is proportional to the number of studies. RHB: conventional rehabilitation; VR: Virtual Reality.

## Results

The following tables show the characteristics of the studies included in the Systematic Review.

Study	Design	Total sample size (EG/CG)	Number of females	Age in years (EG)	Age in years (CG)	Stroke side (left/right)	Stroke type (ischemic/hemorrhagic/both)	Post-stroke time EG/CG (days)	Stroke phase (acute/subacute/chronic)	Baseline MoCA score (EG/CG)	Baseline MMSE score (EG/CG)
Li et al. 2021 <sup>□</sup>	Parallel RCT	200 (100/100)	98	63.3	64.2	Not reported	All ischemic	< 182.5	Acute/subacute	20.04/20.48	21.4/21.03
Ranzani et al. 2020 <sup>□</sup>	Parallel RCT	27 (14/13)	9	70	67.46	15/12	18/8/1	21.98 / 21.56	Acute	Not reported	25.89/23.62
Adornaviciene et al. 2019 <sup>□</sup>	Parallel RCT	42 (17/25)	14	66*	62*	25/17	13/16	49 / 49*	Acute	Not reported	24.05/23.21
Shang et al. 2021 <sup>□</sup>	Parallel RCT	76 (37/39)	35	63.69	64.13	34/42	All ischemic	6.51 / 6.54	Acute	21.84/21.21	Not reported
Taravati et al. 2021 <sup>□</sup>	Parallel RCT	37 (17/20)	9	50.94	55.75	16/21	25/12	332.76 / 384.77	Chronic	20.35/20.25	Not reported
Oh et al. 2019 <sup>□</sup>	Parallel RCT	31 (17/14)	10	57.4	52.6	Not reported	Not reported	Not reported	Not reported	22.7/24.4	Not reported
Kim & Yim 2017 <sup>□</sup>	Parallel RCT	29 (14/15)	10	50.71	51.87	Not reported	Not reported	389.03 / 356.79	Chronic	26.35/25.53	Not reported
Choi et al. 2014 <sup>□</sup>	Parallel RCT	20 (10/10)	10	64.3	64.7	12/8	14/6	20.20 / 23.67	Acute	Not reported	23.7/21.6
Ozen et al. 2021 <sup>□</sup>	Parallel RCT	30 (15/15)	10	62	69.8	19/11	25/5	151.8 / 145.8	Subacute	20.86/17	27.26/25.8
Wilson et al. 2021 <sup>□</sup>	Parallel RCT	17 (10/7)	5	69.9	77.3	11/6	14/3	137.5 / 107.4	Subacute	18.5/17	Not reported
Mao et al. 2020 <sup>□</sup>	Parallel RCT	60 (30/30)	29	54	57	Not reported	47/13	182.5 / 182.5	Subacute/chronic	22/22	Not reported
Lee et al. 2020 <sup>□</sup>	Parallel RCT	36 (18/18)	9	72.1	73.2	28/8	24/12	450.17 / 471.46	Chronic	Not reported	Not reported
Cirstea, Pfito & Levin 2006 <sup>□</sup>	Parallel RCT (3 groups)	35 (14/14/9)	14	EG1=55.7; EG2=59.1	64.5	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Ersoy & Iyigun 2020 <sup>□</sup>	Parallel RCT	40 (20/20)	13	58.25	60.15	19/21	Not reported	954.96 / 1105.65	Chronic	Not reported	Not reported
Daunorvicene et al. 2018 <sup>□</sup>	Parallel RCT	34 (17/17)	12	65.88	65.47	10/14	28/6	60.48 / 67.55	Acute	Not reported	Not reported

\* data is presented as median instead of mean.

Abbreviations: CG: Control Group; EG: Experimental Group; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; RCT: Randomized Controlled Trial

Table 11.9: Characteristics of the included studies according to participant features.

Study	Experimental group	Control group	Dosage	Total amount of treatment (minutes)	Cognitive domains	Cognitive outcome measures
Li et al. 2021 <input type="checkbox"/>	Conventional RHB + strength training which involved hands, fingers, and wrist, elbow and shoulder joints	Conventional RHB including active limb movement and joint activity exercise	20 repetitions per movement, 3-5 cycles each time, twice a day, for 3 months	Not available	Global cognition	MoCA, MMSE
Ranzani et al. 2020 <input type="checkbox"/>	Conventional neurocognitive therapy (Perfetti) + Robot-assisted neurocognitive therapy (ReHapticKnob haptic device)	Conventional neurocognitive therapy (Perfetti)	120 min/day, 3.75 sessions/week for 4 weeks	1800	Global cognition, attention	MMSE, Albert Test
Adomaviciene et al. 2019 <input type="checkbox"/>	Conventional RHB + robot-assisted training (Armeo Spring)	Conventional RHB + VR Kinect-based training	45 min/day, 10 days	450	Global cognition	MMSE, ACE-R
Shang et al. 2021 <input type="checkbox"/>	Conventional RHB + Intensive grip training for both hands using a grip training device with a digital readout (Model HG-2323B)	Conventional RHB	500 repetitions (50 min)/day, 1-5 sessions, ≥3 days/week, 12 weeks	Not available	Global cognition	MoCA
Taravati et al. 2021 <input type="checkbox"/>	Conventional RHB + robot-assisted training (ReoGo)	Conventional RHB including PT, OT and cognitive RHB in case of cognitive impairment	90-105 min/day, 5 days/week, 4 weeks of robot-assisted training + OT. 45 min/day, 2 days/week, 4 weeks of cognitive RHB	2160	Global cognition	MoCA
Oh et al. 2019 <input type="checkbox"/>	VR training (Joystim) + real instrumental training, which involved UL ROM, active or active-assisted functional and ADLs, perception training, including cognitive tasks	Conventional OT including cognitive tasks	30 min/day, 3 days/week, 6 weeks	540	Global cognition	MMSE, MoCA
Kim & Yim 2017 <input type="checkbox"/>	Conventional PT (60 min) + handgrip strength training (15 min) and walking speed training (15 min)	Conventional PT	90 min/day, 3 days/week, 6 weeks	1620	Global cognition, Attention	MoCA, TMT-A, TMT-B, ST
Choi et al. 2014 <input type="checkbox"/>	Conventional RHB (without OT) + VR training (Wii), which involved 12 games for active ROM and UL mobility training	Conventional RHB + OT	30 min/day, 5 days/week, 4 weeks	600	Global cognition, Attention	MMSE, Visual and Auditory CPTs

Ozen et al. 2021 <sup>[1]</sup>	Conventional PT + robot-assisted training (Rejoyce)	Conventional PT + OT based on developing arm and hand coordination, dexterity and ADL training	PT: 60 min/day, 5 days/week, 4 weeks (both groups). Interventions (both groups): 30 min/day, 5 days/week, 4 weeks	1800	Global cognition	MoCA, MMSE
Wilson et al. 2021 <sup>[2]</sup>	Conventional RHB + VR training at home (EDNA-22 system) with 4 goal-based and 3 exploratory movement tasks that require manipulation of handled objects on a tablet	Graded Repetitive Arm Supplementary Program (GRASP) training at home with arm and hand exercises	30 min/day, 3-4 days/week, 8 weeks	720	Global cognition	MoCA
Mao et al. 2020 <sup>[3]</sup>	Conventional RHB + VR training through AO of hand function tasks in ADLs with the Mirror Neuron System Training (MNST V1.0.)	Conv RHB (PT + placement of UL + OT). PT includes ROM, muscle strength and UL movement training	MNST: 20 min/day, 5 days/week, 8 weeks. Conv RHB: 60 min/day, 5 days/week, 8 weeks. OT includes ADLs training for 30 min/day, 5 days/week, 8 weeks	800	Global cognition, reaction time, executive function	MoCA, RT, WCST
Lee et al. 2020 <sup>[4]</sup>	Non-immersive VR training (RAPAEL smart glove) which involved active ROM, coordination and cognition training activities	Recreational activities by computer-generated assignment (exergaming via commercially available video games)	30 min/day, 3 days/week, 8 weeks	720	Attention, perception	TMT (A or B)
Cirstea, Puijo & Levin 2006 <sup>[5]</sup>	EG1 practiced a reaching task with knowledge of results. EG2 practiced the same task with faded knowledge of performance about joint motions	Practiced nonreaching task	60 min/day, 10 days, 2 weeks	1200	Memory, attention, visuospatial ability, executive function	WMSS, RAVLT, ROCFT, CT, WCST, ST, TOL
Ersoy & Iyigun 2020 <sup>[6]</sup>	Bobath + VR training (boxing with 4 levels using the Kinect 360 system)	Bobath + real boxing with 4 levels	Bobath: 30 min/day, 3 days/week, 8 weeks (both groups). Interventions (both): 30 min/day, 3 days/week, 8 weeks	1440	Global cognition	ACE-R
Daunoraviciene et al. 2018 <sup>[7]</sup>	Robot-assisted training (Armeo Spring)	Conventional OT with functional exercises, physical activities and active table games	30 min/day, 5 days/week, 10 days	1500	Global cognition	ACE-R

Abbreviations: AO: Action Observation; ADLs: Activities of Daily Living; ACE-R: Addenbrooke's Cognitive Assessment-Revised; CT: Cancellation test; CPT: Computerized Performance Test; EG: Experimental Group; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; OT: Occupational Therapy; PT: Physical Therapy; ROM: Range of Motion; RT: Reaction Time; RHB: Rehabilitation; RAVLT: Rey Auditory Verbal Learning Test; ROCFT: Rey-Osterrieth Complex Figure Test; ST: Stroop Test; TOL: Tower of London; UL: Upper Limb; VR: Virtual Reality; WMSS: Wechsler Memory Scale Stories; WCST: Wisconsin Card Sorting Test.

Table 11.10: Characteristics of the included studies according to treatment features.

## Ranking of interventions

<b>MoCA</b>		<b>MMSE</b>	
<b>Intervention</b>	<b>Score</b>	<b>Intervention</b>	<b>Score</b>
RHB + Strength training	70.42	RHB + Robot-assisted training	84.41
RHB + Robot-assisted training	60.08	RHB + Strength training	81.86
RHB + VR training	53.48	RHB	29.56
RHB	16.02	RHB + VR training	4.17

Abbreviations: MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; RHB: Rehabilitation; SUCRA: Surface Under the Cumulative Ranking Curve Area (SUCRA); VR: Virtual Reality.

Table 11.11: SUCRA scores for each intervention and outcome measure (MoCA and MMSE).

<b>MoCA</b>				
<b>Rank</b>	<b>RHB</b>	<b>RHB + Robot-assisted training</b>	<b>RHB + Strength training</b>	<b>RHB + VR training</b>
<b>1</b>	0.49%	35.5%	41.68%	22.33%
<b>2</b>	6.56%	26.95%	34.5%	31.98%
<b>3</b>	33.46%	19.85%	17.22%	29.48%
<b>4</b>	59.49%	17.71%	6.6%	16.21%
<b>MMSE</b>				
<b>Rank</b>	<b>RHB</b>	<b>RHB + Robot-assisted training</b>	<b>RHB + Strength training</b>	<b>RHB + VR training</b>
<b>1</b>	0%	53.61%	46.39%	0%
<b>2</b>	0.71%	46%	52.8%	0.4%
<b>3</b>	87.26%	0.39%	0.64%	11.72%
<b>4</b>	12.04%	0%	0.08%	87.88%

Abbreviations: MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; RHB: Rehabilitation; VR: Virtual Reality.

Table 11.12: Rankogram table for each intervention and outcome measure (MoCA and MMSE). Each value represents the probability in percentage that the intervention would rank at every possible position.

## Comparison models

For the MoCA, the random-effects model better fitted (Figure 11.2) with a decrease of 17.098 points in DIC and 20.82 points in Dres, with slightly increase in model complexity (pD from 10.985 to 14.707) without leverage outliers. For the MMSE, the fixed-effects model presented the best fit with a decrease of 1.439 points in DIC and 0.59 points in Dres with slightly decrease in model complexity (pD from 9.805 to 8.956), without leverage outliers (Figure 11.2).

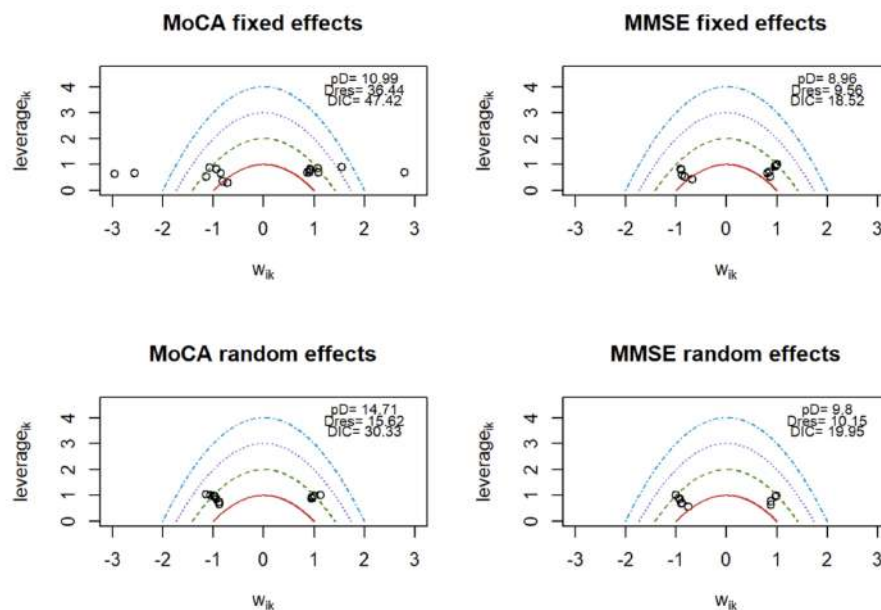


Figure 11.2: Fixed vs random-effects model comparison.

The consistency model had a better fit than the inconsistency model for both the MoCA and the MMSE (Figure 11.3). When posterior mean deviance of consistency versus inconsistency models were plotted, it showed some discrepancies in the MMSE (Figure 11.4). However, node-split showed no significant differences ( $p > 0.05$ ) between the direct and indirect comparisons, which reinforced the consistency between studies (Supplementary Figure 11.5). Both the trace plot and the density plot indicated that the number of iterations was sufficient for an adequate convergence of the models.

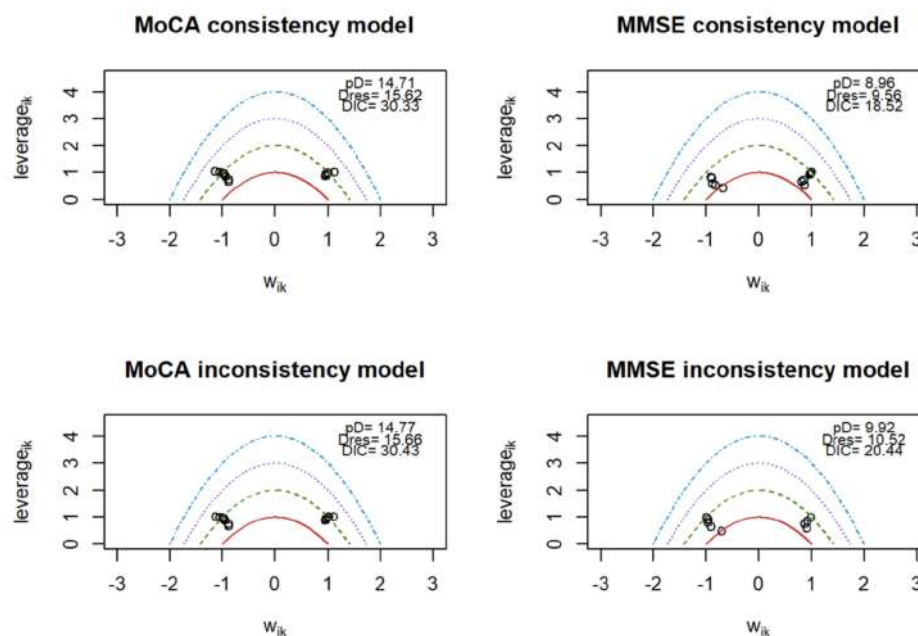


Figure 11.3: Consistency vs inconsistency models comparison.

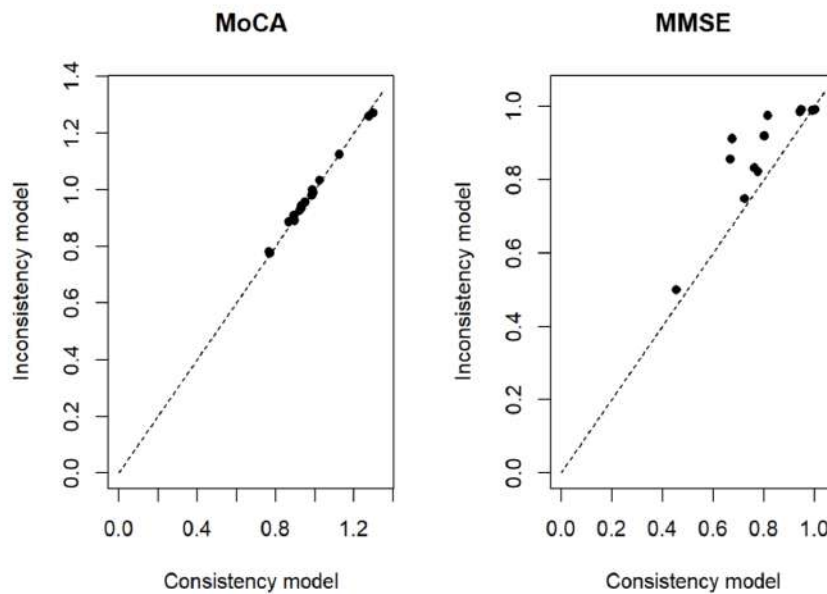


Figure 11.4: Consistency vs. inconsistency posterior mean with and without co-variables model comparison.

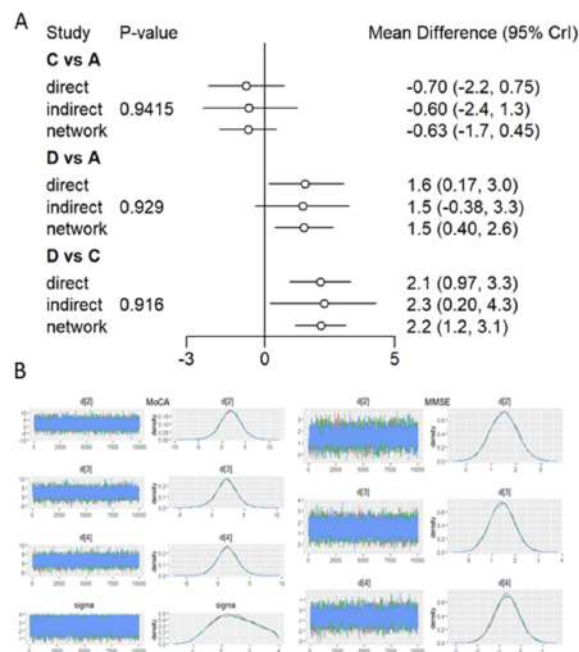


Figure 11.5: A: MMSE nodesplit forest plot. B: Models trace and density plots.

The following figure shows the fixed vs random-effects models with and without co-variables model comparison, to show why the simpler model without co-variables was chosen.

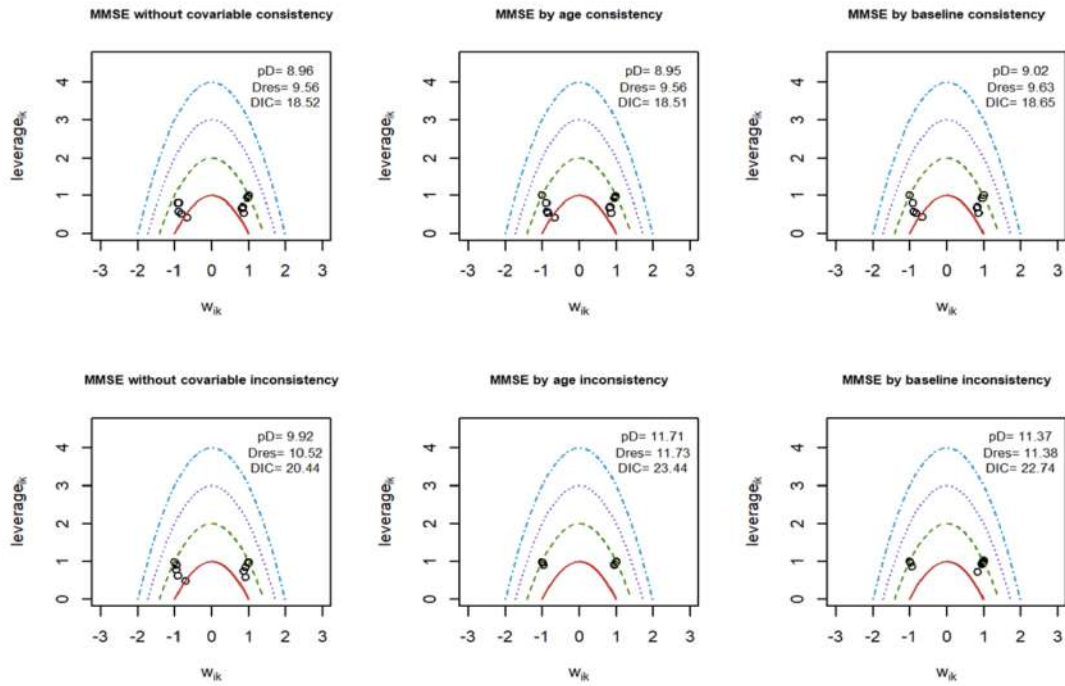


Figure 11.6: Fixed vs random-effects model comparison.

Publication bias

	MoCA		MMSE	
	N of studies	N of patients	N of studies	N of patients
RHB vs. RHB + Robot-assisted training	2	67	2	57
RHB vs. RHB + Strength training	3	305	1	200
RHB vs. RHB + VR training	3	108	2	51
RHB + Robot-assisted vs. RHB + VR training	–	–	1	42

Table 11.13: Comparison characteristics.

Intervention	MoCA				
	N of studies	N of patients	Min score	Max score	Average score
RHB	8	240	18.7	27.4	22.777
RHB + Robot-assisted training	2	32	21.86	23.47	22.715
RHB + Strength training	3	151	23.42	25.96	25.271
RHB + VR training	3	57	21.9	28	26.005
Intervention	MMSE				
	N of studies	N of patients	Min score	Max score	Average score
RHB	5	152	23.98	29.2	24.853
RHB + Robot-assisted training	3	46	26.46	27.8	26.915
RHB + Strength training	1	100	25.4	25.4	25.4
RHB + VR training	3	52	24.36	28.2	25.892

Table 11.14: Intervention characteristics.

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<b>Between-study effects distributions</b>	<b>MoCA</b>	<b>MMSE</b>
Normal	0.079	0.081
Student's T	0.179	0.137
Laplace	0.206	0.191
Slash	0.054	0.111

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Table 11.15: Measure of publication bias.

## Appendix B: Supplementary information of AMBER device

### Instructions for the Strength Task:

"Please place one of your fingers on the corresponding sensor (start with the index finger). When you are ready, press the sensor as hard as you can. Make sure not to use any other fingers; only use the indicated finger. Repeat the process with the other fingers, including the middle finger, ring finger, and pinky finger. Each measurement will be taken three times for each finger."

### Instructions for the Reaction Time Task:

"After a double flash of white lights, the device will emit a series of blue lights. When a light turns on, press the sensor corresponding to that light with the correct finger (for example, sensor 1 with the index finger, sensor 2 with the middle finger, and so on) as quickly as possible. This task will have three difficulty levels: easy, medium, and hard. In the easy level, the lights will appear one after the other, while in the more difficult levels, the sequence will become increasingly complex. Please stay alert and try to respond as quickly as possible during each attempt. Each task ends with a double white flash."

### Instructions for the Memory Task:

"In this task, after a double white flash, you will see a sequence of blue lights turning on one after the other. Your goal is to remember the sequence and, when it ends, reproduce it by pressing the sensors in the same order in which the lights appeared. The sequence length will vary: 3 lights for the easy level, 5 lights for the medium level, and 7 lights for the hard level. Each sequence ends with a double white flash. Try to be as accurate as possible when recalling the sequence."

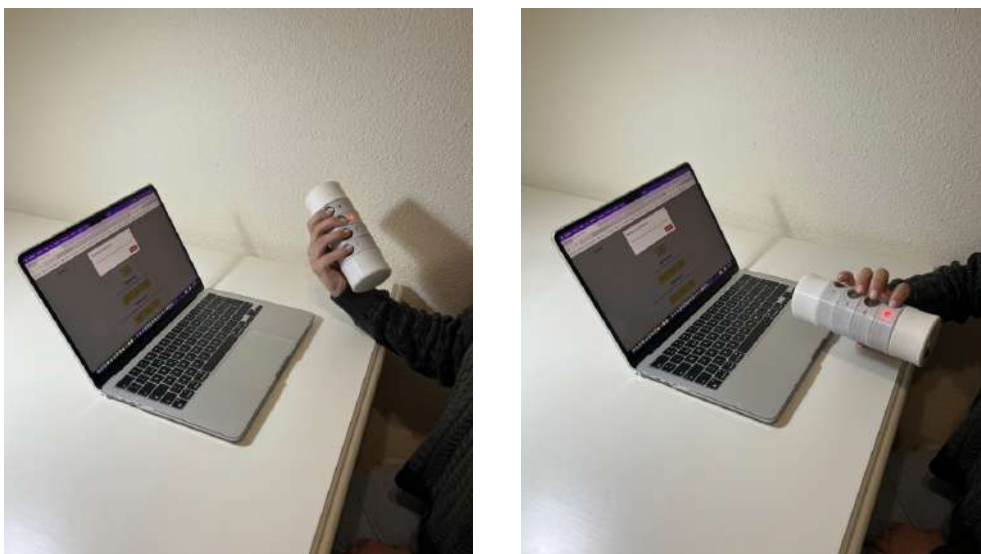


Figure 11.7: Pictures of a healthy volunteer using the AMBER device with two different grips.

## Appendix C: Patent documents

### Patent application receipt



#### Acknowledgement of receipt

We hereby acknowledge receipt of your request for grant of a European patent as follows:

Submission number	300470544	
Application number	EP22383249.4	
File No. to be used for priority declarations	EP22383249	
Date of receipt	21 December 2022	
Your reference	20220745	
Applicant	FUNDACIÓN UNIVERSIDAD FRANCISCO DE VITORIA	
Country	ES	
Title	HAND DEVICE FOR EVALUATING AND RECOVERING AFFECTED COGNITIVE AND MOTOR FUNCTIONS	
Documents submitted	package-data.xml application-body.xml SPECEPO-1.pdf/description.pdf (11 p.) SPECTRANONEP.pdf/translati on.pdf (1 p.)	ep-request.xml ep-request.pdf (5 p.) SPECEPO-2.pdf/drawings.pdf (3 p.) f1002-1.pdf (2 p.)
Submitted by	CN=Silvia Moreno Gordo 63659	
Method of submission	Online	
Date and time receipt generated	21 December 2022, 10:54:46 (CET)	
Official Digest of Submission	96:50:59:C9:79:1A:D8:9B:D9:CB:6E:27:29:25:2D:23:19:78:9F:01	

/Madrid, Oficina Receptora/



## Acknowledgement of receipt

We hereby acknowledge receipt of your request for the processing of an international application according to the Patent Cooperation Treaty as follows:

Submission number	12741040	
PCT application number	PCT/EP2023/086584	
Date of receipt	19 December 2023	
Receiving Office	European Patent Office, The Hague	
Your reference	20231122	
Applicant	FUNDACIÓN UNIVERSIDAD FRANCISCO DE VITORIA	
Number of applicants	2	
Country	ES	
Title	HAND DEVICE FOR EVALUATING AND RECOVERING AFFECTED COGNITIVE AND MOTOR FUNCTIONS	
Documents submitted	eolf-pkda.xml eolf-appb.xml eolf-vlog.xml eolf-appb-P000001.pdf (3 p.)	eolf-requ.xml eolf-fees.xml eolf-othd-000001.pdf (11 p.)
Submitted by	CN=Silvia Moreno Gordo 63659	
Method of submission	Online	
Date and time receipt generated	19 December 2023, 12:03 (CET)	
Message Digest	0A:AC:AA:E3:61:3A:06:2D:C2:68:E1:FD:94:D2:EC:0B:B6:A9:54:DD	

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The access code generated for this application and used to retrieve the priority documents from WIPO's Digital Access Service (DAS) is indicated in the document appended to this acknowledgement of receipt. Please note that the appended document is non-public and will not be published.

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## Patent Cooperation Treaty (PCT)



### DAS access code

To access and retrieve the priority document from WIPO's Digital Access Service (DAS) in respect of

Application number	PCT/EP2023/086584
Applicant	FUNDACIÓN UNIVERSIDAD FRANCISCO DE VITORIA

the European Patent Office has generated the following code:

DAS access code	9BD3
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For further information, see OJ EPO 03/2019.

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<b>0</b>	<b>For receiving Office use only</b>	
<b>0-1</b>	International Application No.	
<b>0-2</b>	International Filing Date	
<b>0-3</b>	Name of receiving Office and "PCT International Application"	
<b>0-4</b>	<b>Form PCT/RO/101 PCT Request</b>	
0-4-1	Prepared Using	PCT Online Filing Version 3.51.000.276e MT/FOP 20141031/0.20.5.24
<b>0-5</b>	<b>Petition</b>	
	The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
<b>0-6</b>	<b>Receiving Office (specified by the applicant)</b>	European Patent Office (EPO) (RO/EP)
<b>0-7</b>	<b>Applicant's or agent's file reference</b>	20231122
<b>I</b>	<b>Title of invention</b>	HAND DEVICE FOR EVALUATING AND RECOVERING AFFECTED COGNITIVE AND MOTOR FUNCTIONS
<b>II</b>	<b>Applicant</b>	
II-1	This person is	Applicant only
II-2	Applicant for	All designated States
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II-7	State of residence	ES
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III-1-7	State of residence	ES

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<b>III-2</b>	<b>Applicant and/or inventor</b>	
III-2-1	This person is	Inventor only
III-2-3	Inventor for	All designated States
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III-3-1	This person is	Inventor only
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<b>III-4</b>	<b>Applicant and/or inventor</b>	
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<b>III-5</b>	<b>Applicant and/or inventor</b>	
III-5-1	This person is	Inventor only
III-5-3	Inventor for	All designated States
III-5-4	Name (LAST, First)	MARTINEZ, Rodrigo
III-5-5	Address	Campus de La Berzosa - C. del Hostal 28240 HOYO DE MANZANARES (Madrid) Spain
<b>III-6</b>	<b>Applicant and/or inventor</b>	
III-6-1	This person is	Inventor only
III-6-3	Inventor for	All designated States
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**PCT REQUEST**

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<b>IV-1</b>	<b>Agent or common representative; or address for correspondence</b> The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	<b>Agent</b>
IV-1-1	Name	<b>HERRERO &amp; ASOCIADOS, S.L.</b>
IV-1-2	Address	<b>Edificio Aqua. Calle Agustín de Foxá 4 - 10 28036 MADRID Spain</b>
IV-1-5	e-mail	<b>notificaciones@herrero.es</b>
IV-1-5(a)	E-mail authorization The receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority are authorized to use this e-mail address, if the Office or Authority so wishes, to send notifications issued in respect of this international application:	<b>exclusively in electronic form (no paper notifications will be sent)</b>
IV-1-6	Agent's registration No.	<b>709</b>
<b>V</b>	<b>DESIGNATIONS</b>	
<b>V-1</b>	<b>The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.</b>	
<b>VI-1</b>	<b>Priority claim of earlier regional application</b>	
VI-1-1	Filing date	<b>21 December 2022 (21.12.2022)</b>
VI-1-2	Number	<b>22383249.4</b>
VI-1-3	Regional Office	<b>EP</b>
<b>VI-2</b>	<b>Priority document request</b> The International Bureau is requested to obtain from a digital library a certified copy of the earlier application(s) identified above as item(s), using, where applicable, the access code(s) indicated:	<b>VI-1 Access code: AB2E</b>
<b>VI-3</b>	<b>Incorporation by reference :</b> where an element of the international application referred to in Article 11(1)(iii)(d) or (c) or a part of the description, claims or drawings referred to in Rule 20.5(a), or an element or part of the description, claims or drawings referred to in Rule 20.5bis(a) is not otherwise contained in this international application but is completely contained in an earlier application whose priority is claimed on the date on which one or more elements referred to in Article 11(1)(iii) were first received by the receiving Office, that element or part is, subject to confirmation under Rule 20.6, incorporated by reference in this international application for the purposes of Rule 20.6.	
<b>VII-1</b>	<b>International Searching Authority Chosen</b>	<b>European Patent Office (EPO) (ISA/EP)</b>

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<b>VII-2</b>	<b>Request to use results of earlier search; reference to that search</b>		
<b>VII-2-1</b>	Filing date	21 December 2022 (21.12.2022)	
<b>VII-2-2</b>	Application Number	22383249.4	
<b>VII-2-3</b>	Country (or regional Office)	EP	
<b>VII-2-4</b>	Statement (Rule 4.12(ii)):	This international application is the same, or substantially the same, as the application in respect of which the earlier search was carried out except, where applicable, that it is filed in a different language.	
<b>VII-2-5</b>	Documents are available to the ISA in a form and a manner acceptable to it, and therefore do not need to be submitted by the applicant to the receiving Office, or to the ISA (Rules 12bis1.(c) and (d) and 12bis.2(b)):	A copy of the results of the earlier search A copy of the earlier application A copy of any document cited in the earlier search results	
<b>VIII</b>	<b>Declarations</b>	Number of declarations	
<b>VIII-1</b>	Declaration as to the identity of the inventor	-	
<b>VIII-2</b>	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
<b>VIII-3</b>	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
<b>VIII-4</b>	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
<b>VIII-5</b>	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
<b>IX</b>	<b>Check list</b>	Number of sheets	Electronic file(s) attached
<b>IX-1</b>	Request (including declaration sheets)	5	✓
<b>IX-2</b>	Description	9	✓
<b>IX-3</b>	Claims	1	✓
<b>IX-4</b>	Abstract	1	✓
<b>IX-5</b>	Drawings	3	✓
<b>IX-6a</b>	Sequence listing part of the description	-	-
<b>IX-7</b>	TOTAL	19	
	<b>Accompanying Items</b>	Paper document(s) attached	Electronic file(s) attached
<b>IX-8</b>	Fee calculation sheet	-	✓
<b>IX-20</b>	<b>Figure of the drawings which should accompany the abstract</b>		
<b>IX-21</b>	<b>Language of filing of the international application</b>	English	

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**PCT REQUEST**

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<b>X-1</b>	<b>Signature of applicant, agent or common representative</b>	/Gustavo Adolfo Gonzalez Peces/
<b>X-1-1</b>	Name	HERRERO & ASOCIADOS, S.L.
<b>X-1-2</b>	Name of signatory	Gustavo Adolfo Gonzalez Peces
<b>X-1-3</b>	Capacity (if such capacity is not obvious from reading the request)	(Representative)

**FOR RECEIVING OFFICE USE ONLY**

<b>10-1</b>	<b>Date of actual receipt of the purported international application</b>	
<b>10-2</b>	<b>Drawings:</b>	
10-2-1	Received	
10-2-2	Not received	
<b>10-3</b>	<b>Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application</b>	
<b>10-4</b>	<b>Date of timely receipt of the required corrections under PCT Article 11(2)</b>	
<b>10-5</b>	<b>International Searching Authority</b>	ISA/EP
<b>10-6</b>	<b>Transmittal of search copy delayed until search fee is paid</b>	

**FOR INTERNATIONAL BUREAU USE ONLY**

<b>11-1</b>	<b>Date of receipt of the record copy by the International Bureau</b>	
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## Description of the invention

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EPO

### SUBJECT OF THE INVENTION

Multi-finger functional grip analysis device and method based on multi-directional disturbance torque control

**[0001]** Technical field

**[0002]** The present disclosure relates to the field of grip test devices, and more particularly to a multi-finger functional grip analysis device and method based on multi-directional disturbance torque control.

**[0003]** Background technique

**[0004]** Hand injury and dysfunction have a serious impact on daily living ability. Grasping test evaluation is an effective means to measure hand dysfunction, so it plays an important role in neurophysiological testing, rehabilitation assessment and hand function damage identification.

**[0005]** The inventor found in the study that there is currently no instrument capable of accurately testing and evaluating the grasping function of the simultaneous participation of the five fingers.

**[0006]** Summary of the invention

**[0007]** The purpose of the embodiments of the present specification is to provide a multi-finger functional grip analysis device based on multi-directional disturbance torque control, which can provide a plurality of different directions of disturbance torque, and can accurately test and record the fingers of the five-finger precise grip under the disturbance torque. The three-dimensional force, three-dimensional moment and pressure center point time series of the fingertip.

**[0008]** The embodiment of the present specification provides a multi-finger functional grip analysis device based on multi-directional disturbance torque control, which is realized by the following technical solutions:

**[0009]** include:

**[0010]** a cylindrical housing in which the fluid is contained;

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- [0011] a torque sensor for detecting a thumb side force is disposed on an inner wall of the cylindrical casing, and a torque sensor for detecting a four-finger side force is disposed on the opposite side of the inner wall of the cylindrical casing;
- [0012] The cylindrical housing is disposed on the base, and is connected to the electromagnet device at the bottom of the base;
- [0013] The electromagnet device is configured to generate a transient abrupt disturbance torque in a specified direction acting on the bottom of the base;
- [0014] The specified direction instantaneous abrupt disturbance torque is a momentary abrupt disturbance torque generated at a plurality of marked positions at equal intervals centered on the center of the base;
- [0015] The torque sensor detects the data signal of the test subject under the action of the instantaneous abrupt disturbance torque, and uses the data signal to process the whole hand grip function evaluation parameter and the grip coupling index between the fingers.
- [0016] The embodiment of the present specification provides a multi-finger grip function test analysis method based on multi-directional disturbance yaw moment sensing control, which is realized by the following technical solutions:
- [0017] include:
- [0018] The grip function test analysis device is grasped by the tester;
- [0019] The bottom of the base of the grip test device receives the instantaneous abrupt disturbance torque in a specified direction;
- [0020] The specified direction instantaneous abrupt disturbance torque is a momentary abrupt disturbance torque generated at a plurality of marked positions at equal intervals centered on the center of the base;
- [0021] For the effect of the instantaneous abrupt disturbance torque in each specified direction, the grip function test analysis device is smoothly raised to the specified height, and the set time is maintained and then placed smoothly to the initial position. After the test, the three-dimensional force of each finger is obtained. Real-time coordinate data signal of torque and pressure center point;

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- [0022] The dynamic coupling complexity between multi-channel signals is calculated by joint recursive quantitative analysis, and the evaluation parameters of the full-hand grip function and the gripping index between the fingers are obtained.
- [0023] Compared with the prior art, the beneficial effects of the present disclosure are:
- [0024] The present disclosure proposes a multi-finger grip function test and analysis device and method based on multi-directional disturbance yaw moment sensing control. The device can provide eight different directions of disturbance torque, and can accurately test and record the three-dimensional force, three-dimensional moment and pressure center point time sequence of the fingertips under the five-finger precision grip under the disturbance torque. At the same time, the device can perform combined recursive quantitative analysis on real-time signals, and use the joint recursive graph to obtain the correlation and complexity parameters of each finger dynamic system, so as to obtain the dynamic index for evaluating the grip function. This instrument can perform functional grip training and evaluation, and the accurate evaluation of the function of the opponent is of great significance.
- [0025] DRAWINGS
- [0026] The accompanying drawings that form a part of this disclosure are used to provide a further understanding of the disclosure, and the description of the present disclosure and the description thereof are not intended to limit the disclosure.
- [0027] 1 is a schematic structural diagram of a gripping function test and analysis device based on multi-directional disturbance torque sensing motion control according to an embodiment of the present disclosure;
- [0028] 2 is a state diagram of a multi-finger precise grip function analysis device after the electromagnet is powered off according to an embodiment of the present disclosure;
- [0029] 3 is a perspective view of a gripping function test and analysis device based on multi-directional disturbance torque sensing motion control according to an embodiment of the present disclosure;
- [0030] 4(a) to 4(h) are schematic diagrams showing the base of the gripping function test and analysis device when the different directions of the disturbance torque are generated in the embodiment of the present disclosure;
- [0031] 5 is an experimental flow chart of an embodiment of the present disclosure;

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- [0032] In the figure, 1 is the top flat cover, 2 is the cylindrical cup wall inside the device, 4 is the thumb side torque sensor, 5-8 is the four four-finger side torque sensor, and 3 is the connecting piece. 9 is a four-finger side curved contact piece, 10 is a thumb-side curved contact piece, 11 is a base, 13 is an elastic rope, 14 is a rated weight, and 14 is an electromagnet.
- [0033] Detailed ways
- [0034] It should be noted that the following detailed description is illustrative and is intended to provide a further description of the disclosure. All technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.
- [0035] It is to be noted that the terminology used herein is for the purpose of describing the particular embodiments, As used herein, the singular " " " " " There are features, steps, operations, devices, components, and/or combinations thereof.
- [0036] Implementation example one
- [0037] This embodiment discloses a multi-finger functional grip analysis device based on multi-directional disturbance torque control, as shown in Figures 1-3, comprising: a hollow cylinder provided with a top flat cover 1 on the thumb side The torque sensor 4 is placed in a relative position with the four four-finger side torque sensors 5, 6, 7, 8 and is fixed to the cylindrical cup wall 2 inside the device, and the sensor and the inner wall of the cup are connected by a connecting piece. The outside of the sensor is closely connected to the thumb side curved contact piece 10 and the four finger side curved contact piece 9, respectively. The inside of the tester is hollow in the shape of a water cup and can hold fluid. The base 11 is preferably cylindrical, and of course may have another shape, and the electromagnet 15 is connected downwardly from the center of the base. Eight equally spaced mark positions centered on the center of the base (ie, starting from the front side, counterclockwise rotating 0°, 45°, 90°, 135°, 180°, 225°, 270°, 315° eight) Position to produce eight specified directions of disturbance torque), the elastic rope 13 is connected, and the rated weight 14 is connected to the end of the rope. The sudden drop of the rated weight is achieved by the on/off of the electromagnet, thereby generating a disturbance torque. The outer wall of the cup is actually composed of five curved pieces that are not in contact with each other, and the contact piece refers to the outermost wall.
- [0038] In an embodiment, the base is internally provided with a partitioned storage box for securing a rope that produces a directional disturbance torque. The storage box is used to place a weight (ie weight) that produces a yaw moment. The device is cylindrical and the contact surface is curved. The purpose is to enable the subject to simulate a columnar grip in daily life and to perform task-

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oriented Testing and training. The square device is a flat surface on both sides, simulating the behavior of the snatching cup or book.

- [0039] In an embodiment, the placement of the five side force and torque sensors on the bracket can be adjusted according to actual needs.
- [0040] In one embodiment, other types of sensors may be employed to obtain real-time air force and torque data from the grip tester, or to place the same pressure sensor in different locations on the tester.
- [0041] In an embodiment, the geometry of the tester equipment can be easily modified as needed, such as being more elliptical.
- [0042] In the embodiment of the present disclosure, the five-finger gripping device is used to detect and record the force, torque, and pressure center point real-time signal data between the five fingers. The instrument body is designed as a cylindrical water cup, which contains five six-dimensional force/torque sensors, which are used to measure real-time signal data of one-hand and five-finger. The sensor at the thumb is in a relative position with the other four fingers, and the distribution position of each sensor conforms to the daily grasping behavior state of the human body.
- [0043] Regarding the generation of multi-directional disturbance torque. The present disclosure is designed with a detachable base under the cup body of the multi-finger precision gripping device, and an electromagnet is connected below the center position of the base to generate a magnetic field. The weight is connected by an elastic rope to eight equally spaced mark positions centered on the midpoint of the base, starting from the front side and counterclockwise rotating 0°, 45°, 90°, 135°, 180°, 225°, 270°. At eight positions of ° and 315°, a magnetic field is generated when the electromagnet is energized, and the weight is adsorbed and fixed to the side, and no force is generated on the elastic rope. When the electromagnet is suddenly powered off, the weight is only dropped downward by the influence of gravity, and the elastic rope is pulled to generate a disturbance torque in a specified direction.
- [0044] The method for generating multi-directional disturbance torque by the device is shown in FIG. The rated weights are connected by elastic ropes, and are fixed in eight equally spaced positions at the center of the base, thereby generating a disturbance torque in a specified direction. Figure 4 (a) - Figure 4 (h) corresponding to the center of the base as the center, from the front side of the counterclockwise rotation 0°, 45°, 90°, 135°, 180°, 225°, 270°, 315°. The eight positions produce disturbing moments in eight different directions. A total of eight tests were performed to

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form eight sets of sequences, each set of three-dimensional forces, three-dimensional moments, and pressure center point data for each finger.

[0045] Implementation example two

[0046] This embodiment discloses a multi-finger grip function test analysis method based on multi-directional disturbance yaw moment sensing control, and the experimental flow is shown in FIG. 5. First collect the subject information and introduce the experimental process. Connect the rated weight to the specified position by the elastic rope, and carry out the grip test of the disturbance torque in a given direction, that is, use the right five fingers to smoothly lift the device, hold it to the specified target height for 10s, and then place it on the table smoothly. initial position. After a test, change the connection position of the rated weight to generate the disturbance torque in different directions for the next test. Test a total of eight times, get eight sets of data, and test the force and moment of each set of data and the original time change of the pressure center point. The signal sequence is stored and analyzed. Get the data as follows:

[0047]  $\{F_{xk}(t), F_{yk}(t), F_{zk}(t), T_{xk}(t), T_{yk}(t), T_{zk}(t), P_{xk}(t), P_{yk}(t)\}$  (1)

[0048] Among them,  $k=1, 2, 3, 4, 5$ , representing the thumb, index finger, middle finger, ring finger and little finger five fingers.  $F_{xk}(t), F_{yk}(t), F_{zk}(t)$  are the three-dimensional force vector time series of a certain finger, and  $T_{xk}(t), T_{yk}(t), T_{zk}(t)$  are the three-dimensional moment vector time series sum of the finger.  $P_{xk}(t)=-T_{yk}(t)/F_{zk}(t)$  and  $P_{yk}(t)=-T_{xk}(t)/F_{zk}(t)$  are the coordinates of the center point of the pressure of the finger.

[0049] For each set of data five fingers of the time series group  $x(k)$ ,  $k = 1, 2, \dots, 5$ , find its joint recursive matrix:

[0050] [image]

[0051] Where  $i, j=1, \dots, N, N$  are the time series length,  $\varepsilon_k$  is a given threshold, indicating the two-point neighbor relationship,

[image]

$\Theta$  is the Herveyside function, and  $\| \cdot \|$  is the phase The Euclidean function used in space. A point with a value of 1 in the JRP chart is shown in black, and a value of 0 is white.

[0052] Recursive density-based measure: RR is the recursion rate, which is used to measure the density of recursive points in the recursive graph, reflecting the recursive frequency of the phase points

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and the degree of convergence of the trajectories in the phase space, which can better distinguish the generated synchronism.

[0053] [image]

[0054] Based on the recursive diagonal measure: DET, when the sequence correlation property is weak, the random or chaotic characteristics will result in a very short diagonal or no diagonal, while the recursive graph of the deterministic sequence will show a longer Diagonal and fewer isolated recursive points.  $P(l)$  is a frequency distribution with a length  $l$  on the diagonal. This measure describes the percentage of recursive points based on the  $45^\circ$  diagonal structure on the recursive graph. The larger the value, the stronger the certainty, and the smaller the equivalent value, the stronger the randomness.

[0055] [image]

[0056] The measure based on the recursive vertical line:  $P(\nu)$  represents the sum of the vertical lines of length  $\nu$  on the recursive graph. The percentage of recursive points in the recursive graph that constitute the vertical line structure in the whole graph is expressed as LAM, which reflects the degree of system state change relatively to some extent, and also reflects the stability of the system from another angle.

[0057] [image]

[0058] [image]

[0059] Using the above parameters for analysis and processing, the RR, DET, and LAM parameters reflect system correlation and complexity. Through the analysis of DET and LAM, the system correlation and complexity are judged initially. Study the correlation of the dynamics system, analyze the complexity of the system, and obtain dynamic indicators to evaluate the coordination and gripping functions between the fingers. The level of RR values of healthy subjects was counted, the mean and distribution range were calculated, and the mean RRH was obtained. The grasp function index GI,

[image]

was defined, where  $\mu$  is the standard deviation of the RR values of the healthy subjects. By performing task-oriented functional grip training and function evaluation, the recovery of hand

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function can be better achieved. The device and method can be used for functional grip training and evaluation, and the accurate evaluation of the opponent's function is of great significance.

- [0060] The present disclosure processes the multi-channel timing signals collected by the device, extracts the correlation and complexity of the effective parameter analysis dynamic system, and obtains an index for evaluating the coordination between the fingers and the full-hand grasping function. The device uses the joint recursive quantitative analysis method to analyze and process the three-dimensional force, three-dimensional moment and pressure center point coordinate data of each finger, and obtain the joint recursive graph and the characteristic parameters reflecting the correlation and complexity of the system, and obtain the full-hand grip function. Evaluate the parameters and the gripping index between each finger.
- [0061] It is used for the testing and evaluation of the full-handed precise grip function, and the diagnosis of the degree of damage of the opponent's function and the recovery of the hand function have important application value. The method uses multi-directional disturbance torque to sense motion control as the basic testing mechanism. The joint recursive quantitative analysis is used to calculate the dynamic coupling complexity between multi-channel signals, and the coordination of the precise grip function of the opponent is tested and evaluated.
- [0062] It is to be understood that in the description of the specification, the descriptions of the terms "one embodiment", "another embodiment", "other embodiment", or "first embodiment to the Nth embodiment" mean Specific features, structures, materials, or characteristics described in connection with the embodiments or examples are included in at least one embodiment or example of the invention. In the present specification, the schematic representation of the above terms does not necessarily mean the same embodiment or example. Moreover, the particular features, structures, and characteristics of the materials described may be combined in any suitable manner in any one or more embodiments or examples.
- [0063] The above description is only a preferred embodiment of the present disclosure, and is not intended to limit the disclosure, and various changes and modifications may be made to the present disclosure. Any modifications, equivalent substitutions, improvements, etc., made within the spirit and scope of the present disclosure are intended to be included within the scope of the present disclosure.

1.A multi-finger functional grip analysis device based on multi-directional disturbance torque control, comprising:

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a cylindrical housing in which the fluid is contained;

a torque sensor for detecting a thumb side force is disposed on an inner wall of the cylindrical casing, and a torque sensor for detecting a four-finger side force is disposed on the opposite side of the inner wall of the cylindrical casing;

The cylindrical housing is disposed on the base, and is connected to the electromagnet device at the bottom of the base;

The electromagnet device is configured to generate a transient abrupt disturbance torque in a specified direction acting on the bottom of the base;

The specified direction instantaneous abrupt disturbance torque is a momentary abrupt disturbance torque generated at a plurality of marked positions at equal intervals centered on the center of the base;

The torque sensor detects the data signal of the test subject under the action of the instantaneous abrupt disturbance torque, and uses the data signal to process the whole hand grip function evaluation parameter and the grip coupling index between the fingers.

2.The multi-finger-actuated grip analysis device based on multi-directional disturbance torque control according to claim 1, wherein the torque sensor of the thumb side force and the torque sensor of the four-finger side force respectively pass the corresponding connecting piece and the cylinder. The outer side of the shaped housing is in fixed contact with the plane.

3.The multi-finger disturbance grip control multi-finger functional grip analysis device according to claim 1, wherein the electromagnet device comprises an electromagnet, a rated weight and an elastic rope, and the base is connected downward from the center. The electromagnet connects the rated weights from the elastic ropes to several marked positions at equal intervals in the center of the base.

4.The multi-finger disturbance torque control multi-finger functional grip analysis apparatus according to claim 1, wherein the base is cylindrical.

5.A multi-finger grip function test analysis method based on multi-directional disturbance yaw moment sensing control, characterized in that it comprises:

The grip function test analysis device is grasped by the tester;

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The bottom of the base of the grip test device receives the instantaneous abrupt disturbance torque in a specified direction;

The specified direction instantaneous abrupt disturbance torque is a momentary abrupt disturbance torque generated at a plurality of marked positions at equal intervals centered on the center of the base;

For the effect of the instantaneous abrupt disturbance torque in each specified direction, the grip function test analysis device is smoothly raised to the specified height, and the set time is maintained and then placed smoothly to the initial position. After the test, the three-dimensional force of each finger is obtained. Real-time coordinate data signal of torque and pressure center point;

The dynamic coupling complexity between multi-channel signals is calculated by joint recursive quantitative analysis, and the evaluation parameters of the full-hand grip function and the gripping index between the fingers are obtained.

6.The multi-finger grasping function test and analysis method based on multi-directional disturbance yaw moment sensing control according to claim 5, wherein the tested force and torque and the original time-varying signal sequence of the pressure center point are stored and analyzed. Get the data as follows:

$$\{F_{xk}(t), F_{yk}(t), F_{zk}(t), T_{xk}(t), T_{yk}(t), T_{zk}(t), P_{xk}(t), P_{yk}(t)\}$$

Among them,  $k=1, 2, 3, 4, 5$ , representing the thumb, index finger, middle finger, ring finger and little finger five fingers.  $F_{xk}(t), F_{yk}(t), F_{zk}(t)$  are the three-dimensional force vector time series of a finger,  $T_{xk}(t), T_{yk}(t), T_{zk}(t)$  are the three-dimensional moment vector time sequence of the finger, and  $P_{xk}(t)=-T_{yk}(t)/F_{zk}(t)$  and  $P_{yk}(t)=-T_{xk}(t)/F_{zk}(t)$  are the coordinates of the center point of the pressure of the finger.

7.The multi-finger gripping function test and analysis method based on multi-directional disturbance yaw moment sensing control according to claim 5, wherein the time series group  $x(k), k=1, 2$ , for each group of data five fingers. ...,5, find its joint recursive matrix:

[image]

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Where  $i, j=1, \dots, N, N$  are time series lengths,  $\varepsilon_k$  is a given threshold, indicating the relationship between points and points,

[image]

$\Theta$  is the Hervey side function,  $\|\cdot\|$  It is the Euclidean function used in the phase space. The point with a value of 1 in the JRP graph is shown as black, and the value at 0 is white.

8.The multi-finger grasping function test analysis method based on multi-directional disturbance yaw moment sensing control according to claim 5, wherein the recursive density-based measure:  $RR_x$ ,  $y$  is a recursion rate, and is used for measuring a recursive point in the recursive graph. The density reflects the phase recursive frequency and the degree of convergence of the trajectory in the phase space, which can better distinguish the generated synchronism;

[image]

9.The method for testing and analyzing multi-finger grip function based on multi-directional disturbance yaw moment sensing control according to claim 5, characterized in that: based on the recursive diagonal measure: DET, when the sequence correlation characteristic is weak, random or chaotic The characteristics will result in very short diagonals or no diagonals, while the recursive graph of the deterministic sequence will show longer diagonals and fewer isolated recursive points,  $P(l)$  on the diagonal a frequency distribution of length  $l$ ; this measure describes the percentage of recursive points based on the  $45^\circ$  diagonal structure on the recursive graph. The larger the value, the stronger the certainty, and the smaller the equivalent value, the stronger the randomness;

[image]

The measure based on the recursive vertical line:  $P(\nu)$  represents the sum of the vertical lines of length  $\nu$  on the recursive graph, and the percentage of the recursive points in the recursive graph that constitute the vertical line structure in the whole figure is expressed as LAM, reflecting to some extent The degree of relative change in system state also reflects the stability of the system from another angle;

[image]

[image]

## Patent drawings

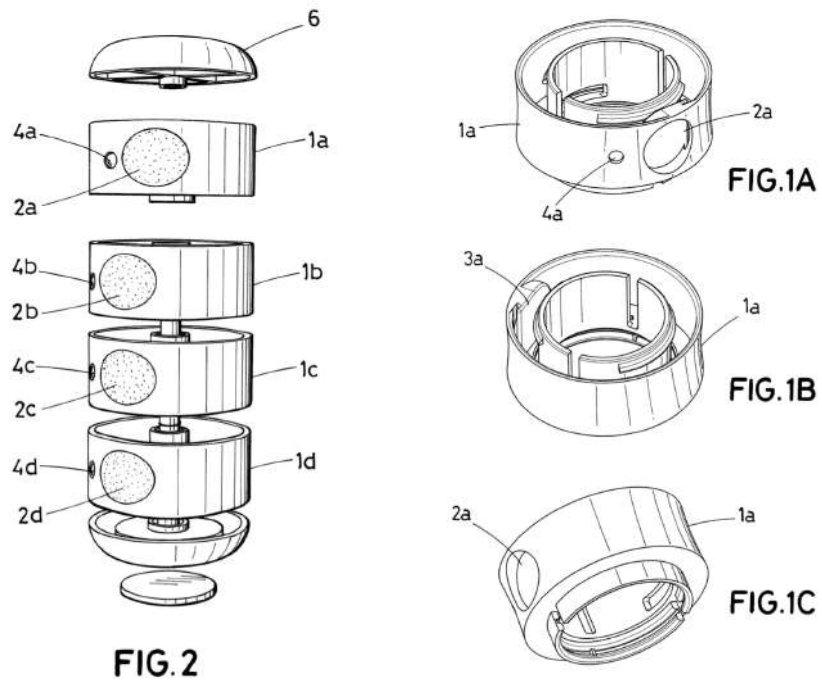


Figure 11.8: Drawings of the structural design of the device.

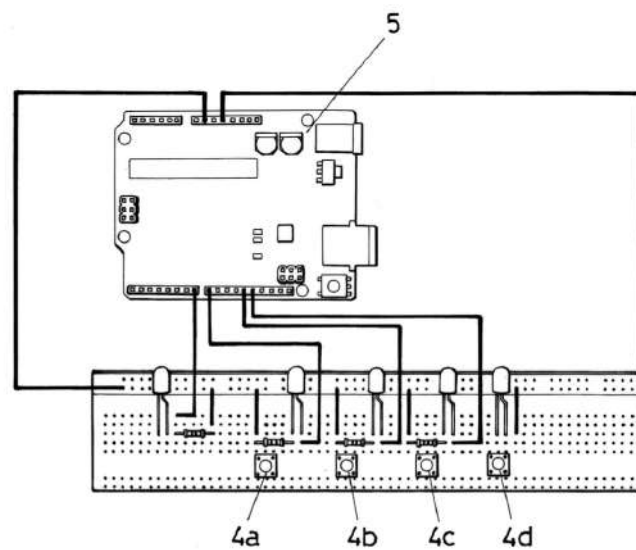


FIG. 3

Figure 11.9: Drawing of the connections of the electronic components of the device.

## Appendix D: Approval of the Research Ethics Committee



**Nº CEIm: 22/495**

### DICTAMEN DEL COMITÉ DE ÉTICA DE LA INVESTIGACIÓN

Dña. **DULCE MARIA UGALDE DIEZ**, Secretaria del Comité de Ética de la Investigación con medicamentos del HOSPITAL UNIVERSITARIO 12 DE OCTUBRE.

#### CERTIFICA

Que este Comité en la reunión celebrada el día 20/12/2022 ha evaluado la propuesta del investigador para que se realice el proyecto de investigación, titulado: *Diseño y validación de un dispositivo para evaluación cognitiva y motora de miembro superior en pacientes con Daño Cerebral: Dispositivo AMBER (portable and Modular device for comprehensive Brain Evaluation and Rehabilitation) / AMBER (Artefacto Modular portátil para la rehabilitación y Evaluación integral cerebral)*

TIPO DOCUMENTO	VERSIÓN
Protocolo	v.2 - 5 diciembre 2022
Hoja Información de Paciente - paciente	v. 2 - 5 diciembre 2022
Hoja Información de Paciente - voluntarios sanos	v. 2 - 5 diciembre 2022
CI	v. 2 - 5 diciembre 2022

Entendiendo que dicho estudio se ajusta a las normas éticas esenciales y criterios deontológicos que rigen en este Centro, cumpliendo los requisitos metodológicos necesarios y las normas de funcionamiento interno del Comité. Se han ponderado los aspectos metodológicos éticos y legales y se recogerá la decisión adoptada en el acta correspondiente.

Este Comité **INFORMA FAVORABLEMENTE** a la realización de dicho proyecto.

El estudio será realizado en el **HOSPITAL BEATA MARIA ANA** por **JUAN PABLO ROMERO MUÑOZ, ROBERTO ÁLVAREZ FERNÁNDEZ** y **CARMEN SÁNCHEZ AVILA** como Investigadores Principales.

Lo que firmo en Madrid, a 20 de diciembre de 2022

Fecha: 2022.12.20  
15:38:36 +01'00'

Firmado.: Dra. **DULCE MARIA UGALDE DIEZ**  
Secretaria del CEIm Hospital Universitario 12 de Octubre

### **ANEXO I: COMPOSICIÓN DEL CEIm**

**Nº CEIm:** 22/495

**Título:** Diseño y validación de un dispositivo para evaluación cognitiva y motora de miembro superior en pacientes con Daño Cerebral: Dispositivo AMBER (portABLE and Modular device for comprehensive Brain Evaluation and Rehabilitation) / AMBER (Artefacto Modular portátil para la rehaBilitación y Evaluación integral ceRebral)

**Investigador Principal:** JUAN PABLO ROMERO MUÑOZ, ROBERTO ÁLVAREZ FERNÁNDEZ y CARMEN SÁNCHEZ AVILA

**Dña. MARÍA UGALDE DIEZ,** Secretaria del Comité de Ética de Investigación con medicamentos del **HOSPITAL UNIVERSITARIO 12 DE OCTUBRE.**

Hace constar que:

1. En la reunión ordinaria celebrada el día 20/12/2022, se decidió emitir el informe correspondiente al estudio de referencia.
2. En dicha reunión se cumplieron los requisitos establecidos en la legislación vigente Real Decreto 1090/2015 para que la decisión del citado CEIm sea válida
3. El CEIm del Hospital Universitario 12 de Octubre, tanto en su composición como en sus PNTs, cumple con las normas de BPC (CPMP/ICH/135/95)
4. La composición del CEIm del Hospital Universitario 12 de Octubre en la citada fecha, era la siguiente:

**Presidente:**

- MARIA DEL PUY GOYACHE GOÑI - Farmacéutico Adjunto de Farmacia Hospitalaria

**Vicepresidente:**

- SARAHI ELIZABETH VALDEZ ACOSTA - Farmacóloga Clínica

**Secretario:**

- DULCE MARIA UGALDE DIEZ - Dra. en Ciencias Biológicas

**Vocales:**

- ELENA PUERTO GARCIA MARTIN - Médico Cardiología
- TYCHO STEPHAN BAUMANN - Médico Hematología
- LUIS MANUEL MANSO SANCHEZ - Médico Oncología
- CRISTINA MARTIN-ARRISCADO ARROBA - Licenciada Estadística
- MARIA LUISA ALBELDA DE LA HAZA - Licenciada Derecho
- CANDELAS LOPEZ LOPEZ - Diplomado Universitario en Enfermería
- GONZALO CARREÑO GOMEZ-TARRAGONA - Médico Hematología
- JORGE ADEVA ALFONSO - Médico Oncología
- RAFAEL SAN JUAN GARRIDO - Médico Microbiología
- ROBERTO RODRIGUEZ JIMENEZ - Médico Psiquiatría
- ANA ISABEL JIMENEZ UBIETO - Médico Hematología

- GEMA RUIZ HURTADO - Comisión de Investigación
- MARIA DEL MAR ESPINO HERNANDEZ - Pediatra de Atención Primaria
- M<sup>a</sup> DEL CARMEN RIESCO MARTINEZ - Médico Oncología
- MARIA DE LAS MERCEDES CATALAN GONZALEZ - Médico Intensivista
- RAQUEL SIGUIN GOMEZ - Farmacéutica Atención Primaria
- LAURA LEMA ROSO - Médico Oncología
- YOLANDA RODRIGUEZ GIL - Médico Anatomía Patológica
- FRANCISCO JAVIER MAZUECOS GOMEZ - Trabajador Social Ayuntamiento Madrid
- SAGRARIO ALEGRE ALONSO - Coordinadora AECC
- MARIA DEL PILAR HERNANDEZ SUAREZ - Diplomado Universitario en Enfermería
- RAQUEL SOPEÑA SUTIL - Médico Urología
- DAVID SANCHEZ GUZMAN - Médico Atención Primaria
- MARIA MONTSERRAT PILAS PEREZ - Diplomado Universitario en Enfermería
- ELENA GUTIERREZ SOLIS - Médico Nefrología
- MAGDALENA ABAD GRAN - Facultativo Especialista Ginecología y Obstetricia

## **ANEXO II: COMPROMISOS CONTRAÍDOS POR EL INVESTIGADOR CON RESPECTO AL COMITÉ DE ÉTICA DE LA INVESTIGACIÓN**

Se recuerda al investigador que la ejecución del estudio le supone los siguientes compromisos con el Comité:

- Ejecutar el estudio con arreglo a lo especificado en el protocolo, tanto en los aspectos científicos como en los aspectos éticos.
- Notificar al Comité todas las modificaciones o enmiendas en el estudio y solicitar una nueva evaluación de las relevantes.
- Enviar al Comité un informe final al término de la ejecución del estudio. Este informe deberá incluir los siguientes apartados:
  - o Número de registro del estudio en bases de datos públicas de proyectos de investigación, si procede.
  - o Memoria final del estudio, la enviada a las agencias reguladoras
  - o Publicación/es científica/s generada/s por el estudio
  - o Información (tipo y modo) transmitida a los sujetos del estudio sobre los resultados de la investigación y sobre los que afecten directamente a su salud (si procede)

## Appendix E: Healthy volunteer affiliation form

### ESTUDIO AMBER

*FORMULARIO DE FILIACION DE VOLUNTARIOS SANOS (INFORMACIÓN CONFIDENCIAL)*

Investigador: .....

Fecha de la 1ª evaluación (TEST): .....

Fecha de la 2ª evaluación (RETEST): .....

Nº de anonimización asignado (Código): .....

#### Datos del voluntario:

Género:

.....

Fecha de nacimiento (edad): .....

Nivel educativo (básico/intermedio/superior): .....

Dominancia manual (diestro/zurdo): .....

Afecciones:

- Hipertensión
- Dislipemia
- Diabético
- Alteración de la coagulación
- Cardiopatía isquémica
- Fumador
- Bebedor
- Otras drogas

Contacto:

.....

## Appendix F: Informed consents for validation study

**Título: Estudio Amber. Diseño y validación de un dispositivo para evaluación cognitiva y motora de miembro superior en pacientes con Daño Cerebral: Dispositivo AMBER (portable and Modular device for comprehensive Brain Evaluation and Rehabilitation) / AMBER (Artefacto Modular portátil para la rehabilitación y Evaluación integral cerebral)**

### CONSENTIMIENTO INFORMADO PARA EL PROCEDIMIENTO DE EVALUACIÓN MOTORA

#### Descripción del estudio:

Las escalas de evaluación del deterioro motor aportan información sobre el estado/recuperación de habilidades motoras con datos objetivos.

#### Procedimiento:

Consistirá en la realización de 9 pruebas validadas en la valoración del deterioro motor.

1. Uso de dinamómetro para evaluar la fuerza de agarre.
2. Uso de pinch forcé para evaluar la fuerza de prensión de los dedos de la mano.
3. Grooved Pegboard, para evaluar la destreza manipulativa, coordinación óculo-manual y otras funciones de la extremidad superior.

El investigador le explicará detenidamente en qué consiste cada prueba para que pueda colaborar adecuadamente.

#### Molestias:

La evaluación con estas pruebas puede suponer alguna molestia en términos de fatiga leve o moderada

#### Beneficios:

Los beneficios que le brinda la participación en este proyecto incluyen el hecho de tener datos cuantitativos en cuanto a la función motora de su miembro superior. Su participación en el proyecto posibilitará que el grupo de investigadores desarrolle estrategias de rehabilitación que reviertan en una mejor calidad de vida de los pacientes con déficits motores en miembro superior.

#### Confidencialidad:

Todos los registros se mantendrán de forma que su participación en este proyecto sea confidencial, de tal manera que, si los resultados del estudio se hacen públicos, su nombre o datos confidenciales no aparecerán en ningún momento. Los datos obtenidos en este estudio serán usados exclusivamente para extraer conclusiones científicas. Su

identidad sólo será conocida por el responsable del proyecto en el centro y sus colaboradores.

Discontinuación del estudio:

Su participación en este proyecto es totalmente voluntaria y usted puede abandonar el mismo en el momento que lo desee y sin que ello repercuta en su asistencia sanitaria futura.

**DERECHOS DE LOS INVESTIGADORES DEL ESTUDIO**

Los investigadores tienen el derecho de interrumpir su participación en el estudio si determinan que no es adecuado que continúe en él, si pudiera ser peligroso para usted continuar o si no sigue los procedimientos del estudio como le indican los investigadores.

Autorización

Por este documento solicitamos su autorización para realizarle el procedimiento, así como a usar imágenes e información de su Historia Clínica con fines docentes o científicos. Su anonimato será respetado.

Declaración y firmas

Antes de firmar este documento, si desea más información o tiene cualquier cuestión, no dude en preguntarnos.

Información básica relativa a la protección de sus datos de carácter personal:

El responsable del tratamiento de sus datos es la Universidad Francisco de Vitoria (UFV).

Conforme a lo dispuesto en la LOPD (Ley de Protección de Datos) Reglamento (UE) 2016/679 del Parlamento europeo y del Consejo de 27 de abril de 2016 de Protección de Datos (RGPD). Se informa de que sus datos serán tratados e incorporados al fichero de la FUNDACIÓN UNIVERSIDAD FRANCISCO DE VITORIA con fines de gestión, investigación científica y docencia. Sólo podrían ser cedidos a organismos autorizados. Puede ejercitar sus derechos de acceso, rectificación, supresión, oposición, limitación del tratamiento y portabilidad mediante un escrito dirigido a la Secretaría General de la Universidad Francisco de Vitoria, Ctra. M-515 Pozuelo-Majadahonda Km. 1,800; 28223, Pozuelo de Alarcón (Madrid), o al correo electrónico [dpd@ufv.es](mailto:dpd@ufv.es)

*Relativo al paciente*

D./D.ª ..... con D.N.I .....

He sido suficientemente informado del procedimiento que se me va a realizar, explicándoseme sus riesgos, complicaciones y alternativas, lo he comprendido y he tenido el tiempo suficiente para valorar mi decisión. Por tanto, estoy satisfecho con la información recibida. Por ello, doy mi consentimiento para que se me realice dicho procedimiento por el especialista responsable. Mi aceptación es voluntaria y puedo revocar este consentimiento cuando lo crea oportuno, sin que esta decisión repercuta en mis cuidados posteriores.

Sé que estoy siendo atendido en un Hospital Universitario  AUTORIZO  SÍ  NO para la utilización de imágenes e información de la Historia Clínica resultante del procedimiento con fines docentes o científicos, tratándose de forma confidencial y anónima según dispone la legislación vigente.

Firma del paciente

Fecha ...../...../.....

*Relativo al especialista*

El Fisioterapeuta, ha informado al paciente y/o tutor o familiar del objeto y naturaleza del procedimiento que se le va a realizar, explicándole los riesgos, complicaciones y alternativas posibles.

Firma del Fisioterapeuta

Fecha ...../...../.....

*Relativo a los familiares y tutores*

El paciente D./D.ª..... no tiene capacidad para decidir en este momento.

D./D.ª..... con D.N.I..... y en calidad de..... he sido informado/a suficientemente del procedimiento que se le va a realizar. Por ello, doy expresamente mi consentimiento. Mi aceptación es voluntaria y puedo retirar este consentimiento cuando lo crea oportuno.

**Título: Estudio Amber. Diseño y validación de un dispositivo para evaluación cognitiva y motora de miembro superior en pacientes con Daño Cerebral: Dispositivo AMBER (portable and Modular device for comprehensive Brain Evaluation and Rehabilitation) / AMBER (Artefacto Modular portátil para la rehabilitación y Evaluación integral cerebral)**

**CONSENTIMIENTO INFORMADO PARA EL PROCEDIMIENTO DE EVALUACIÓN COGNITIVA**

Descripción del estudio:

Las escalas de evaluación de la función cognitiva aportan información sobre el desempeño de las distintas funciones de su cerebro.

Procedimiento:

Consistirá en la realización de 5 pruebas validadas en la valoración cognitiva.

1. Test de MoCA para evaluar las funciones ejecutivas, la capacidad visuoespacial, la memoria, la atención, la concentración y la memoria de trabajo, el lenguaje y la orientación.
2. Test de Stroop, para medir el control atencional.
3. TMT (Test del trazo (Trail Making Test)) para evaluar la atención, la flexibilidad del pensamiento y la habilidad visuoespacial.
4. Simbol Digit Modality Test, para evaluar la velocidad de procesamiento y la velocidad motora
5. Medición de tiempos de reacción a través de pruebas previamente validadas en estudios de nuestro grupo.

El investigador le explicará detenidamente en qué consiste cada prueba para que pueda colaborar adecuadamente.

Beneficios:

Los beneficios que le brinda la participación en este proyecto incluyen el hecho de tener datos cuantitativos en cuanto a su estado cognitivo. Su participación en el proyecto posibilitará que el grupo de investigadores desarrolle estrategias de rehabilitación que reviertan en una mejor calidad de vida de los pacientes con déficits motores en miembro superior.

Confidencialidad:

Todos los registros se mantendrán de forma que su participación en este proyecto sea confidencial, de tal manera que, si los resultados del estudio se hacen públicos, su

nombre o datos confidenciales no aparecerán en ningún momento. Los datos obtenidos en este estudio serán usados exclusivamente para extraer conclusiones científicas. Su identidad sólo será conocida por el responsable del proyecto en el centro y sus colaboradores.

#### Discontinuación del estudio:

Su participación en este proyecto es totalmente voluntaria y usted puede abandonar el mismo en el momento que lo desee y sin que ello repercuta en su asistencia sanitaria futura.

### **DERECHOS DE LOS INVESTIGADORES DEL ESTUDIO**

Los investigadores tienen el derecho de interrumpir su participación en el estudio si determinan que no es adecuado que continúe en él, si pudiera ser peligroso para usted continuar o si no sigue los procedimientos del estudio como le indican los investigadores.

#### Autorización

Por este documento solicitamos su autorización para realizarle el procedimiento, así como a usar imágenes e información de su Historia Clínica con fines docentes o científicos. Su anonimato será respetado.

#### Declaración y firmas

Antes de firmar este documento, si desea más información o tiene cualquier cuestión, no dude en preguntarnos.

Información básica relativa a la protección de sus datos de carácter personal:

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*Relativo al paciente*

D./D.ª .....con D.N.I .....

He sido suficientemente informado del procedimiento que se me va a realizar, explicándoseme sus riesgos, complicaciones y alternativas, lo he comprendido y he tenido el tiempo suficiente para valorar mi decisión. Por tanto, estoy satisfecho con la información recibida. Por ello, doy mi consentimiento para que se me realice dicho procedimiento por el especialista responsable. Mi aceptación es voluntaria y puedo revocar este consentimiento cuando lo crea oportuno, sin que esta decisión repercuta en mis cuidados posteriores.

Sé que estoy siendo atendido en un Hospital Universitario AUTORIZO SÍ NO para la utilización de imágenes e información de la Historia Clínica resultante del procedimiento con fines docentes o científicos, tratándose de forma confidencial y anónima según dispone la legislación vigente.

Firma del paciente

Fecha ...../...../.....

*Relativo al especialista*

El Fisioterapeuta, ha informado al paciente y/o tutor o familiar del objeto y naturaleza del procedimiento que se le va a realizar, explicándole los riesgos, complicaciones y alternativas posibles.

Firma del Fisioterapeuta

Fecha ...../...../.....

*Relativo a los familiares y tutores*

El paciente D./D.ª ..... no tiene capacidad para decidir en este momento.

D./D.ª ..... con D.N.I..... y en calidad de..... he sido informado/a suficientemente del procedimiento que se le va a realizar. Por ello, doy expresamente mi consentimiento. Mi aceptación es voluntaria y puedo retirar este consentimiento cuando lo crea oportuno.

**Título: Estudio Amber. Diseño y validación de un dispositivo para evaluación cognitiva y motora de miembro superior en pacientes con Daño Cerebral: Dispositivo AMBER (portAble and Modular device for comprehensive Brain Evaluation and Rehabilitation) / AMBER (Artefacto Modular portátil para la rehaBilitación y Evaluación integral ceRebral)**

**CONSENTIMIENTO INFORMADO PARA LA EVALUACIÓN CON EL DISPOSITIVO AMBER**

Descripción del estudio:

Las evaluación cognitiva y motora a través de las tareas de AMBER requerirá su interacción con el dispositivo siguiendo ordenes sencillas, de acuerdo a su desempeño obtendremos una evaluación objetiva de su capacidad motora y cognitiva.

Procedimiento:

Consistirá en la realización de 3 pruebas con el dispositivo que consisten en presionar los botones del dispositivo con diferentes dedos en respuesta a las luces que se vayan encendiendo en el mismo.

El investigador le explicará detenidamente en qué consiste cada prueba para que pueda colaborar adecuadamente.

Beneficios:

Los beneficios que le brinda la participación en este proyecto incluyen el hecho de tener datos cuantitativos en cuanto a su estado cognitivo. Su participación en el proyecto posibilitará que el grupo de investigadores desarrolle estrategias de rehabilitación que reviertan en una mejor calidad de vida de los pacientes con déficits motores en miembro superior.

Confidencialidad:

Todos los registros se mantendrán de forma que su participación en este proyecto sea confidencial, de tal manera que, si los resultados del estudio se hacen públicos, su nombre o datos confidenciales no aparecerán en ningún momento. Los datos obtenidos en este estudio serán usados exclusivamente para extraer conclusiones científicas. Su identidad sólo será conocida por el responsable del proyecto en el centro y sus colaboradores.

Discontinuación del estudio:

Su participación en este proyecto es totalmente voluntaria y usted puede abandonar el mismo en el momento que lo desee y sin que ello repercuta en su asistencia sanitaria futura.

#### **DERECHOS DE LOS INVESTIGADORES DEL ESTUDIO**

Los investigadores tienen el derecho de interrumpir su participación en el estudio si determinan que no es adecuado que continúe en él, si pudiera ser peligroso para usted continuar o si no sigue los procedimientos del estudio como le indican los investigadores.

#### Autorización

Por este documento solicitamos su autorización para realizarle el procedimiento, así como a usar imágenes e información de su Historia Clínica con fines docentes o científicos. Su anonimato será respetado.

#### Declaración y firmas

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Información básica relativa a la protección de sus datos de carácter personal:

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#### *Relativo al paciente*

D./D.ª.....con D.N.I .....

He sido suficientemente informado del procedimiento que se me va a realizar, explicándoseme sus riesgos, complicaciones y alternativas, lo he comprendido y he tenido el tiempo suficiente para valorar mi decisión. Por tanto, estoy satisfecho con la información recibida. Por ello, doy mi consentimiento para que se me realice dicho

procedimiento por el especialista responsable. Mi aceptación es voluntaria y puedo revocar este consentimiento cuando lo crea oportuno, sin que esta decisión repercuta en mis cuidados posteriores.

Sé que estoy siendo atendido en un Hospital Universitario AUTORIZO SÍ NO para la utilización de imágenes e información de la Historia Clínica resultante del procedimiento con fines docentes o científicos, tratándose de forma confidencial y anónima según dispone la legislación vigente.

Firma del paciente

Fecha ...../...../.....

*Relativo al especialista*

El Fisioterapeuta, ha informado al paciente y/o tutor o familiar del objeto y naturaleza del procedimiento que se le va a realizar, explicándole los riesgos, complicaciones y alternativas posibles.

Firma del Fisioterapeuta

Fecha ...../...../.....

*Relativo a los familiares y tutores*

El paciente D./D. <sup>a</sup>..... no tiene capacidad para decidir en este momento.

D./D. <sup>a</sup>..... con D.N.I..... y en calidad de..... he sido informado/a suficientemente del procedimiento que se le va a realizar. Por ello, doy expresamente mi consentimiento. Mi aceptación es voluntaria y puedo retirar este consentimiento cuando lo crea oportuno.

# Appendix G: Paper Archives of Physical Medicine and Rehabilitation Journal



Archives of Physical Medicine and Rehabilitation

Journal homepage: [www.archives-pmr.org](http://www.archives-pmr.org)

Archives of Physical Medicine and Rehabilitation 2024;105:1770–83



## REVIEW ARTICLE (META-ANALYSIS)

### Effects of Hand Motor Interventions on Cognitive Outcomes Post-stroke: A Systematic Review and Bayesian Network Meta-analysis



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#### Abstract

**Objective:** To synthesize the evidence on the effects of hand rehabilitation (RHB) interventions on cognition post-stroke and compare their efficacy.

**Data Sources:** PubMed, Embase, Cochrane, Scopus, Web of Science, and CINAHL were searched from inception to November 2022.

**Data Selection:** Randomized controlled trials conducted in adults with stroke where the effects of hand motor interventions on any cognitive domains were assessed.

**Data Extraction:** Data were extracted by 2 independent reviewers. A Bayesian Network Meta-analysis (NMA) was applied for measures with enough studies and comparisons. Risk of bias was assessed with the Cochrane Risk of Bias tool.

**Data Synthesis:** Fifteen studies were included in qualitative synthesis, and 11 in NMA. Virtual reality (VR) (n=7), robot-assisted (n=5), or hand-grip strength (n=3) training were the experimental interventions and conventional RHB (n=14) control intervention. Two separate NMA were performed with MoCA (n=480 participants) and MMSE (n=350 participants) as outcome measures. Both coincided that the most probable best interventions were robot-assisted and strength training, according to SUCRA and rankogram, followed by conventional RHB and VR training. No significant differences between any of the treatments were found in the MoCA network, but in the MMSE, robot-assisted and strength training were significantly better than conventional RHB and VR. No significant differences between robot-assisted and strength training were found nor between conventional RHB and VR.

**Conclusions:** Motor interventions can improve MoCA/MMSE scores post-stroke. Most probable best interventions were robot-assisted and strength training. Limited literature assessing domain-specific cognitive effects was found.

Archives of Physical Medicine and Rehabilitation 2024;105:1770–83

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Stroke is a leading cause of adult disability which currently affects more than 143 million people worldwide.<sup>1</sup> There are around

12.2 million new cases of stroke each year, most of which will result in both motor and cognitive chronic impairment.<sup>1,2</sup>

Most stroke survivors experience some degree of upper limb (UL) motor deficit in the acute phase, which will make them unable to perform certain activities of daily living (ADLs) in the long term.<sup>3</sup> The most common UL motor sequelae of stroke are muscle weakness and sensory alterations, which hinder normal movement kinematics, leading to residual functional impairment

This work was supported by the Spanish Ministry of Science and Innovation (grant No. PID2020-113222GB-1000110001000). This organization was not involved in study design, collection, analysis and interpretation of data, writing of the report (or decision to submit the article for publication).

Disclosures: None.

0003-9993/36 - see front matter © 2024 by the American Congress of Rehabilitation Medicine.  
<https://doi.org/10.1016/j.apmr.2023.12.013>

in 70% of cases.<sup>4</sup> These alterations frequently affect hand function by provoking hand shaping difficulties, modifying muscle tone or impairing dexterous and fragmented finger movement.<sup>5,6</sup>

In addition to motor disability, cognitive function deterioration is a highly prevalent consequence of stroke which will affect 4 in 10 survivors in the first year of evolution.<sup>7</sup> Specifically, around 80% of patients with stroke have cognitive impairment in 1 or more cognitive domains, with attention, short-term memory, and executive function being among the most frequently affected cognitive abilities.<sup>8,9</sup> These impairments have a remarkable negative effect on health-related quality of life of stroke survivors, deeply affecting their independence in ADLs.<sup>10</sup> However, the European Stroke Organization and the European Academy of Neurology, in their 2021 guidelines, highlighted the little attention paid to these symptoms both in clinical practice and research,<sup>11</sup> despite their great importance in functional performance.<sup>12</sup>

Over 20% of stroke survivors exhibit concurrent motor and cognitive impairment.<sup>13</sup> In fact, there is evidence of common pathophysiological and structural correlates of cognitive and motor deficits among stroke survivors. For instance, there is work suggesting that motor performance is associated with global cognition, memory, and executive function.<sup>13</sup> Shared underlying neural pathways between motor and cognitive functions could explain the concurrent decline in cognition and motor performance after stroke.<sup>14</sup> These alterations can be caused directly by the stroke lesion or by structural and functional changes that appear at a certain distance from the injury but affect connected areas (diaschisis) and/or wide neural networks.<sup>15</sup> Furthermore, ample observational evidence suggests that there is a tight relation between UL function and global cognitive level,<sup>16,17</sup> and that cognitive demands influence hand motor performance.<sup>18</sup> More precisely, cognitive status might influence on motor variables such as reaction time or coordination, which in consequence affect performance of fine manual tasks and has been used to detect cognitive decline.<sup>19</sup> There are also studies showing that cognitive impairment can affect physical rehabilitation (RHB)<sup>20</sup> and that both executive and attention dysfunctions post-stroke can affect the amount of improvement in hand motor function after training.<sup>21</sup>

Traditionally, stroke recovery strategies have been delivered separately by means of motor and cognitive RHB.<sup>21</sup> Both approaches have typically been applied at different recovery times, dosages, and by different neurorehabilitation professionals, without considering the concomitant effects they might have on each other's domains.<sup>22</sup> There is, notwithstanding, a body of research suggesting overlapping effects across these interventions.

#### List of abbreviations:

ACE-R	Addenbrooke's Cognitive Assessment-Revised
ADLs	activities of daily living
CI	credible interval
MD	mean difference
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
NMA	network meta-analysis
RCT	randomized controlled trial
RHB	rehabilitation
RoB	Risk of Bias
SUCRA	surface under the cumulative ranking curve
UL	upper limb
VR	virtual reality

Hand strength training has been shown to positively affect cognition in healthy adults<sup>23</sup> and in mild cognitive impairment.<sup>24</sup> Moreover, UL motor RHB can improve some specific cognitive dimensions such as executive functioning and attention in other neurologic disorders like Parkinson's disease.<sup>25</sup> However, cumulative evidence on the effects of hand motor interventions on cognitive status in people with stroke is strikingly lacking.

Several systematic reviews have shown that different modalities of general exercise training such as strength, aerobic, or ergometer training have significant positive effects on cognition post-stroke,<sup>26-28</sup> although this is a line of research that remains largely under-investigated<sup>29</sup> and controversy does exist.<sup>30</sup> Similarly, UL motor RHB through task-specific and robot-assisted training has been suggested to potentiate the effects of neuropsychological RHB on common post-stroke deficits such as hemineglect.<sup>31,32</sup> Functional reorganization of attentional networks through use-dependent plasticity might explain these beneficial outcomes.<sup>33</sup>

Despite previous preclinical<sup>34</sup> and clinical<sup>35</sup> work suggests that concurrent improvements in cognitive function after hand motor RHB in people with stroke might exist, the evidence to date has not been previously summarized. Therefore, the objective of this systematic review was to quantitatively synthesize the evidence regarding the effect of hand physical RHB on cognition post-stroke. We aimed to determine the concomitant cognitive effects of motor interventions through compiling randomized controlled trials (RCTs) that investigated improvements in hand function variables through motor RHB, in which cognitive variables were also assessed.

## Methods

This systematic review followed the PRISMA 2020 statement<sup>36</sup> and was prospectively registered in PROSPERO (CRD42022377865). The reporting of the Bayesian Network Meta-Analysis (NMA) followed the PRISMA extension for this type of studies<sup>37</sup> and the ISPOR-AMCP-NPC guidelines.<sup>38</sup>

### Eligibility criteria

Studies were eligible if a hand motor RHB intervention was used in a RCT targeting any of the following for people with hemiparesis post-stroke: hand function, hand strength, finger strength, hand dexterity, and finger dexterity. Additionally, the studies had to provide at least 1 outcome measure of a cognitive variable concomitant with hand motor variables and not to provide formal cognitive interventions as part of the experimental conditions, or deliver interventions with cognitive-motor aspects such as mental representation techniques (eg, motor imagery). We defined a formal cognitive intervention as that delivered by a licensed neuropsychologist. There were no restrictions on the outcome measures, but we only considered the following cognitive assessments for inclusion: cognitive function brief evaluation through screening tests, attention, memory, executive functioning, praxis, and perception. We only selected articles written in English and/or Spanish. Publication dates were the earliest available within each database.

We defined hand motor interventions as therapeutic approaches aiming to produce an improvement of hand function through movement and/or practice of functional tasks, without training cognitive aspects as a direct objective of the intervention. This

included all physical therapy and occupational therapy interventions. Non-invasive brain stimulation interventions were excluded even if applied only on brain motor areas as there is evidence of concurrent cognitive improvements through these techniques. Control group interventions included all types of alternative treatments, including conventional RHB (defined as “techniques that have been widely established and practiced in the fields of physical therapy and occupational therapy, including exercises, activities, and interventions designed to improve hand function, coordination, and dexterity, or UL motor function), usual care, placebo or no intervention, non-invasive brain stimulation, and pharmacologic interventions.

The population was defined as adults (>18 years) with hand function deficits after a stroke. There were no restrictions regarding stroke type, lesion location, or evolution phase. Participants with any other neurologic diseases were excluded. People with clinically defined dementia were also excluded.

### Information sources and search strategy

Electronic searches were conducted in 6 databases from inception to November 2022: PubMed, Web of Science, Scopus, Cochrane Library (CENTRAL), CINAHL, and Embase. The searches were run between 1 and 30 November 2022.

The search strategy was undertaken considering the combination of the following concepts: (1) stroke, (2) hand motor interventions, (3) hand motor function variables, and cognitive domains including (4) global cognition, (5) attention, (6) memory, (7) executive functioning, (8) praxis, and (9) perception. The first 3 concepts were always present in all electronic searches and were combined with each cognitive domain separately to increase sensitivity. Search strings varied slightly depending on the MeSH terms within each database. The detailed search strategy can be found in supplemental table S1 (available online only at <http://www.archives-pmr.org/>).

### Study selection process

Screening was based on the following hierarchy. For titles and abstracts: (1) study design was not observational; (2) participants were adults with stroke receiving hand motor interventions; (3) outcome measures of hand function variables were provided; (4) at least 1 cognitive outcome measure was provided. For full texts: (1) study design was RCT; (2) cognitive interventions were not administered as part of the experimental condition; (3) cognitive outcomes were reported pre- and post-intervention; (4) the publication was peer-reviewed.

Duplicates were first removed using the “deduplicator” online tool.<sup>39</sup> The software ranked duplicates as “extremely likely”, “highly likely”, and “likely” based on the amount of their shared information. This process was manually checked by M.M.V. to ensure the software did not remove any potential study. After duplicate removal 2 authors (L.V.L. and M.M.V.) screened titles, abstracts, and full texts independently. In case of disagreement, consensus was reached by discussion and if this was not possible a third independent author decided.

### Data collection and qualitative synthesis

A data extraction table was developed in Microsoft Excel to collect information from the studies that met the inclusion criteria. Data items included (1) the number and characteristics of the

participants, including age, sex, type of stroke (ischemic or hemorrhagic), lesion location (cortical or subcortical and blood vessel affected where available), and time after stroke onset (in weeks if possible), that defined the recovery phase (acute≤3 months, subacute=3–6 months, chronic≥6 months), global cognitive function and global UL motor function, were collected and divided into the intervention and control group wherever possible; (2) the features of the interventions, including nature (conventional RHB or other interventions) and dosage (minutes per session, sessions per week, total number of sessions, and total number of hours of therapy); (3) the outcome measures for hand motor variables and cognition (including global cognition, attention, memory, executive functioning, praxis, and perception separately where available); (4) the main results of the trial, including pre-post within-group differences and between-group differences at post-intervention.

### Quantitative synthesis: Bayesian Network Meta-Analysis

For continuous outcome measures with enough number of comparisons, a Bayesian NMA was applied. The statistical analyses were performed in R (version 4.1.3, R Core Team 2023) using the “BUGSne”<sup>40</sup> and “gemte”<sup>41</sup> packages. Bayesian NMA can be used to obtain a posterior probability distribution of all the relative treatment effects, which allows to quantify the uncertainty of parameter estimates, and to rank all the treatments in the network.<sup>42</sup>

The Bayesian NMA was computed using the Markov Chain Monte Carlo simulation algorithm with Gibbs sampling. For each outcome measure, the mean difference (MD) was computed as effect size. In the studies in which the results were reported as 95% confidence intervals, data were transformed into SD using appropriate formulas.<sup>43</sup>

The effectiveness of the treatments was analyzed using the surface under the cumulative ranking curve (SUCRA) and inspection of the rankogram, where larger values reflect greater probability of effectiveness for each intervention. Direct comparisons between treatments were analyzed as MD with 95% credible intervals (CIs) through a league table, and forest plots if statistically significant differences were found.

In each NMA, the selection of a random or fixed effects model and presence of inconsistency were assessed, by analyzing the leverage graph (defined as posterior mean residual deviance of each study arm minus the deviance at the posterior mean of the fitted values) vs Bayesian residual deviance ( $w$ ) defined as each study arm contribution to the posterior mean deviance of the model. Likewise, deviance was evaluated specifically with the mean of the residual deviance (Dres), effective number of parameters or sum of leverages (pD), and Deviance Information Criteria (DIC) defined as the sum of Dres and pD. In these statistics, the lower the value, the better fit of the model.<sup>44</sup> In the case that a variable presented enough comparisons, the presence of inconsistency was also evaluated using the node-split method, which allows detecting the presence of significant differences between direct and indirect comparisons. In addition, if discrepancies were detected in the plot of posterior mean of consistency vs inconsistency models, an additional meta regression model was applied adding as covariables age and baseline scores. The convergence of the posterior distributions of the parameters through Markov Chain Monte Carlo sampling was evaluated

with the trace plot of mean of each comparison over all the iterations, as well as with the density plot of the subsequent effect size estimate.

Publication bias was assessed with D measure based on the Robust Bayesian Copas selection model defined as negligible (<0.25), moderate (0.25-0.5), high (0.5-0.75), and very high (>0.75).<sup>45</sup>

### Risk of bias and methodological quality assessment

The Risk of Bias 2 (RoB2.0) tool from the Cochrane Collaboration was used. RoB2.0 is structured into a fixed set of domains of bias, focusing on trial design, conduct, and reporting. Each assessment focuses on a specific result from a RCT. Within each domain, a series of questions aim to elicit information about features of the trial that are relevant to RoB. A judgment about the RoB arising from each domain is proposed by an algorithm and can be "Low" or "High" or express "Some concerns". The overall RoB result is the least favorable assessment across the domains of bias.

The PEDro scale was used to assess the methodological quality. PEDro is a 11-item scale where aspects such as presence of eligibility criteria, randomization and allocation concealment, similarity between groups at baseline, blinding (subjects, therapists, and assessors), percentage of dropouts, intention-to-treat analysis, between-group comparisons, and provision of point measures and measures of variability are considered from a RCT. Each item is scored as "yes" or "no" if the study sufficiently describes the aspect of interest. The first item does not count toward the total score, and therefore the scale has a maximum score of 10 points, where higher scores indicate better quality.

Both the RoB2.0 and PEDro scale were administered by 2 independent raters (L.V.L. and M.M.V.). Concordance between them was tested using the weighted kappa coefficient, interpreted as no agreement, none to slight, fair, moderate, substantial, and almost perfect agreement if kappa  $\leq$  0, 0.01-0.2, 0.21-0.4, 0.41-0.6, 0.61-0.8, and 0.81-1, respectively.<sup>46</sup>

## Results

### Selection process

The flow of information is shown in figure 1. From 4540 records initially identified, 2269 were duplicated and 2164 were excluded after title screening. From the remaining 107 studies, 57 were excluded after abstract screening. Fifty full texts were sought for retrieval and 39 were assessed for eligibility, of which 15 were finally included in qualitative synthesis<sup>47-61</sup> and 11 in quantitative synthesis via NMA.<sup>47-57</sup>

### Study characteristics

All the included studies were RCTs with parallel design which implemented hand motor interventions in people with stroke and collected at least 1 cognitive outcome measure pre-post intervention.

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### Participant characteristics

A total of 714 participants (287 women, mean age=62.35 years) were included (table 1). The average age was 61.60 years in the experimental groups and 63.11 years in the control groups. Regarding the stroke side, data from 349 of the 714 participants were retrieved. Among the reported data, 189 (54.15%) of the strokes were on the left side. In the case of the type of stroke, not all the data were reported either. Data from 365 participants were reported and 284 (77.8%) of the strokes were ischemic and 81 were hemorrhagic. The post-stroke time was heterogeneous, including patients in the acute, subacute, and chronic phase, with the average time of the reported data of 234.69 days, which corresponds to chronic stroke. However, most participants were in the acute or subacute phase (446 of 648 participants from the data reported).

### Intervention characteristics

Seven studies combined conventional RHB with virtual reality (VR) training, 5 studies with robot-assisted training, and 3 studies with strength training as experimental interventions (table 2). Conventional RHB alone was the main control intervention (13 studies), either combining occupational therapy and physical therapy or in isolation. One study combined RHB with VR training as the control intervention.

The amount of therapy received was matched between experimental and control groups. Intervention's dosage ranged between 30 and 120 minutes/day, 1-5 sessions/week, and 2-12 weeks. The total amount of treatment received ranged between 450 and 2160 minutes.

### Outcome measures

Five studies used the Montreal Cognitive Assessment (MoCA) as the unique global cognitive measure, and 3 studies utilized the Mini-Mental State Examination (MMSE). Three studies provided data from both the MoCA and MMSE simultaneously. Three studies utilized the Addenbrooke's Cognitive Assessment-Revised (ACE-R) as an overall score for global cognition, 1 of which also utilized the MoCA. Two of the studies utilizing the ACE-R overall score also provided data according to its specific cognitive domains (attention, memory, fluency, language, and visuospatial).

Six studies assessed different cognitive domains with specific outcome measures, including the Albert Test (n=1), the Trail Making Test (n=2), the Wisconsin Card Sorting Test (n=1), a Reaction Time paradigm (n=1), visual and auditory Computerized Performance Tests (n=1), and the Stroop Test (n=2). Therefore, attention, memory, and executive functioning were the main cognitive domains assessed.

### Risk of bias and methodological quality assessment

Regarding RoB, most of the included studies (n=10) were categorized as "some concerns" in overall RoB and the remaining (n=5) as "high" (fig 2A). In Domain 1, 7 studies had low RoB and 8 studies "some concerns" (fig 2B). In Domain 2, 10 studies had "some concerns" and 5 had high RoB. In Domain 3, all of the studies had low RoB. In Domain 4, only 1 study had "some concerns", the remaining (n=14) had low RoB. In Domain 5, 10 studies had low RoB and 5 studies "some concerns". Concordance between

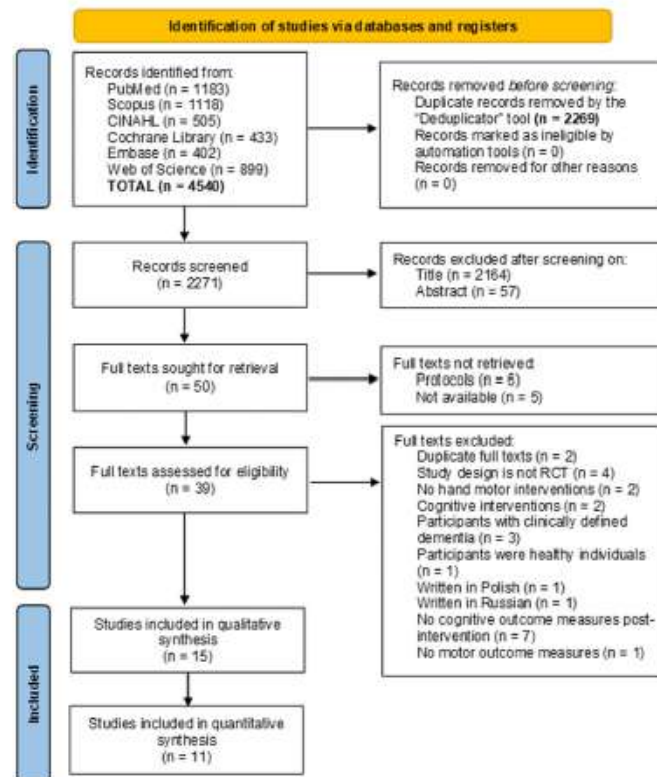


Fig 1 PRISMA 2020 flow diagram.

raters was moderate in overall bias ( $\kappa=0.5$ , 95% CI=0.14-0.86; supplemental fig S7; available online only at <http://www.archives-pmr.org/>).

Regarding methodological quality according PEDro (table 3), studies presented fair to good methodological quality (range: 4-7 points, mean=6, SD=1). Items 5, 6, and 7 (blinding of subjects, therapists, and assessors) and 9 (intention-to-treat) were the least sufficiently addressed. Concordance between raters was substantial for the total score ( $\kappa=0.72$ , 95% CI=0.46-0.98; supplemental fig S8 available online only at <http://www.archives-pmr.org/>).

### Effects of hand motor interventions on global cognition: qualitative synthesis

Most studies (n=8) found positive effects of conventional RHB on global cognition, whereas 4 studies did not find significant within-group differences between pre- and post-intervention. All studies that examined the effects of VR training found positive effects on global cognition. Three studies that examined the effects of robot-assisted training found positive effects on global cognition,

whereas 2 did not. Finally, positive effects of strength training interventions on global cognition were found in all the studies which implemented this treatment (n=3).

### Effects of hand motor interventions on specific cognitive domains: qualitative synthesis

One study did not find statistically significant effects of either robot-assisted training + conventional RHB or RHB alone on the Albert Test, without between-group differences. One study obtained positive effects of strength training + conventional RHB on the Trail Making Test-B (but not on Trail Making Test-A) and on the Stroop Test, although the group receiving conventional RHB alone only showed statistically significant effects on the Stroop Test. No between-group differences were found in either case. One study found positive effects of VR training + conventional RHB on the Trail Making Test. One study found positive effects of VR training + conventional RHB on the Wisconsin Card Sorting Test and Reaction Times, as well as conventional RHB alone.

**Table 1** Characteristics of the included studies according to participant features

Study	Design	Total Sample Size (EG/CG)	Number of Women	Age in Years (EG)	Age in Years (CG)	Stroke Side (Left/Right)	Stroke Type (Ischemic/Hemorrhagic/Both)	Post-stroke Time (days) EG/CG	Stroke Phase (Acute/Subacute/Chronic)	Baseline MoCA Score (EG/CG)	Baseline MMSE Score (EG/CG)
Li et al., 2021 <sup>15</sup>	Parallel RCT	200 (100/100)	98	63.3	64.2	Not reported	All ischemic	<182.5	Acute/subacute	20.04/20.48	21.4/21.03
Ranzani et al., 2020 <sup>44</sup>	Parallel RCT	27 (14/13)	9	70	67.46	15/12	18/8/1	21.98/21.56	Acute	Not reported	25.89/23.62
Adomavičienė et al., 2019 <sup>47</sup>	Parallel RCT	42 (17/25)	14	66*	62*	25/17	13/16	49/49*	Acute	Not reported	24.05/23.21
Shang et al., 2021 <sup>48</sup>	Parallel RCT	76 (37/39)	35	63.69	64.13	34/42	All ischemic	6.51/6.54	Acute	21.84/21.21	Not reported
Taravati et al., 2021 <sup>41</sup>	Parallel RCT	37 (17/20)	9	50.94	55.75	16/21	25/12	332.76/384.77	Chronic	20.35/20.25	Not reported
Oh et al., 2019 <sup>30</sup>	Parallel RCT	31 (17/14)	10	57.4	52.6	Not reported	Not reported	Not reported	Not reported	22.7/24.4	Not reported
Kim & Yim, 2017 <sup>22</sup>	Parallel RCT	29 (14/15)	10	50.71	51.87	Not reported	Not reported	389.03/356.79	Chronic	26.35/25.53	Not reported
Choi et al., 2014 <sup>52</sup>	Parallel RCT	20 (10/10)	10	64.3	64.7	12/8	14/6	20.20/23.67	Acute	Not reported	23.7/21.6
Ozen et al., 2021 <sup>51</sup>	Parallel RCT	30 (15/15)	10	62	69.8	19/11	25/5	151.8/145.8	Subacute	20.86/17	27.26/25.8
Wilson et al., 2021 <sup>54</sup>	Parallel RCT	17 (10/7)	5	69.9	77.3	11/6	14/3	137.5/107.4	Subacute	18.5/17	Not reported
Mao et al., 2020 <sup>55</sup>	Parallel RCT	60 (30/30)	29	54	57	Not reported	47/13	182.5/182.5	Subacute/chronic	22/22	Not reported
Lee et al., 2020 <sup>38</sup>	Parallel RCT	36 (18/18)	9	72.1	73.2	28/8	24/12	450.17/471.46	Chronic	Not reported	Not reported
Cristea, Pitto & Levin, 2006 <sup>37</sup>	Parallel RCT (3 groups)	35 (14/14/9)	14	EG1=55.7; EG2=59.1	64.5	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Ercay & Lygiun, 2020 <sup>49</sup>	Parallel RCT	40 (20/20)	13	58.25	60.15	19/21	Not reported	95.4/96/1105.65	Chronic	Not reported	Not reported
Daunoravičienė et al., 2018 <sup>39</sup>	Parallel RCT	34 (17/17)	12	65.88	65.47	10/14	28/6	60.48/67.55	Acute	Not reported	Not reported

Abbreviations: CG, control group; EG, experimental group; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; RCT, randomized controlled trial.  
 \* Data are presented as median instead of mean.

**Table 2** Characteristics of the included studies according to interventions' features and outcome measures

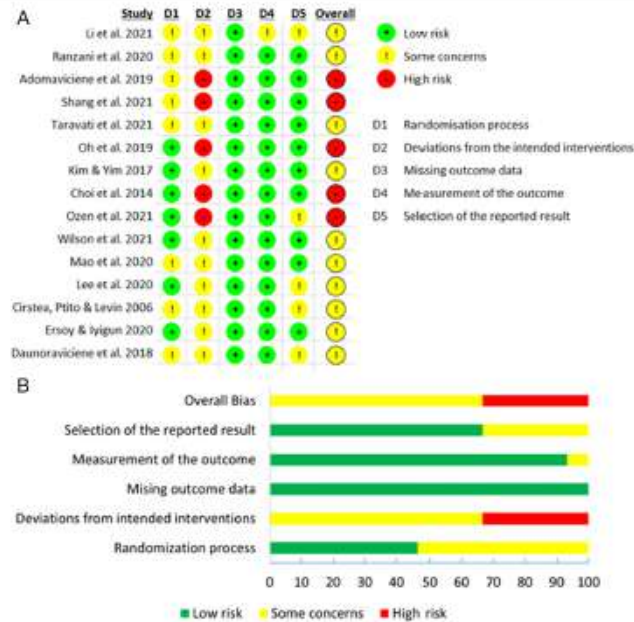
Study	Experimental Group	Control Group	Dosage	Total Amount of Treatment (minutes)	Cognitive Domains	Cognitive Outcome Measures
Li et al, 2021 <sup>43</sup>	Conventional RHB+strength training which involved hands, fingers, and wrist, elbow, and shoulder joints	Conventional RHB including active limb movement and joint activity exercise	20 repetitions per movement, 3-5 cycles each time, twice a day, for 3 months	Not available	Global cognition	MoCA, MMSE
Ranzani et al, 2020 <sup>44</sup>	Conventional neurocognitive therapy (Perfetti)+robot-assisted neurocognitive therapy (ReHapticKnob haptic device)	Conventional neurocognitive therapy (Perfetti)	120 min/day, 3.75 sessions/week for 4 weeks	1800	Global cognition, attention	MMSE, Albert Test
Adomaviciene et al, 2019 <sup>45</sup>	Conventional RHB+robot-assisted training (Armeo Spring)	Conventional RHB+VR Kinect-based training	45 min/day, 10 days	450	Global cognition	MMSE, ACE-R
Shang et al, 2021 <sup>46</sup>	Conventional RHB+intensive grip training for both hands using a grip training device with a digital readout (Model H0-2323B)	Conventional RHB	500 repetitions (50 min)/day, 1-5 sessions, ≥3 days/week, 12 weeks	Not available	Global cognition	MoCA
Taravati et al, 2021 <sup>47</sup>	Conventional RHB+robot-assisted training (ReoGo)	Conventional RHB including PT, OT, and cognitive RHB in case of cognitive impairment	90-105 min/day, 5 days/week, 4 weeks of robot-assisted training+OT, 45 min/day, 2 days/week, 4 weeks of cognitive RHB	2160	Global cognition	MoCA
Oh et al, 2019 <sup>48</sup>	VR training (Joystick)+real instrumental training, which involved UL ROM, active or active-assisted functional and ADLs, perception training, including cognitive tasks	Conventional OT including cognitive tasks	30 min/day, 3 days/week, 6 weeks	540	Global cognition	MMSE, MoCA
Kim & Yim, 2017 <sup>49</sup>	Conventional PT (60 min)+handgrip strength training (15 min) and walking speed training (15 min)	Conventional PT	90 min/day, 3 days/week, 6 weeks	1620	Global cognition, Attention	MoCA, TMT-A, TMT-B, ST
Choi et al, 2014 <sup>12</sup>	Conventional RHB (without OT)+VR training (Wii), which involved 12 games for active ROM and UL mobility training	Conventional RHB+OT	30 min/day, 5 days/week, 4 weeks	600	Global cognition, Attention	MMSE, Visual and Auditory CPTs
Ozen et al, 2021 <sup>5</sup>	Conventional PT+robot-assisted training (ReJoyce)	Conventional PT+OT based on developing arm and hand coordination, dexterity and ADL training	PT: 60 min/day, 5 days/week, 4 weeks (both groups). Interventions (both groups): 30 min/day, 5 days/week, 4 weeks	1800	Global cognition	MoCA, MMSE

(continued on next page)

**Table 2 (Continued)**

Study	Experimental Group	Control Group	Dosage	Total Amount of Treatment (minutes)	Cognitive Domains	Cognitive Outcome Measures
Wilson et al., 2021 <sup>54</sup>	Conventional RHB+VR training at home (EDNA-22 system) with 4 goal-based and 3 exploratory movement tasks that require manipulation of hand/feet objects on a tablet	Graded Repetitive Arm Supplementary Program (GRASP) training at home with arm and hand exercises	30 min/day, 3–4 days/week, 8 weeks	720	Global cognition	MoCA
Mao et al., 2020 <sup>55</sup>	Conventional RHB+VR training through AD of hand function tasks in ADs with the Mirror Neuron System Training (MNST V1.0.)	Conv RHB (PT+placement of UL+OT). PT includes ROM, muscle strength, and UL movement training	MNST: 20 min/day, 5 days/week, 8 weeks. Conv RHB: 60 min/day, 5 days/week, 8 weeks. OT includes ADLs training for 30 min/day, 5 days/week, 8 weeks	800	Global cognition, reaction time, executive function	MoCA, RT, WCST
Lee et al., 2020 <sup>56</sup>	Non-immersive VR training (RAPAEL smart glove) which involved active ROM, coordination, and cognition training activities	Recreational activities by computer-generated assignment (eergaming via commercially available video games)	30 min/day, 3 days/week, 8 weeks	720	Attention, perception	TMT (A or B)
Cirstea, Pitoa, & Levin, 2006 <sup>57</sup>	EG1 practiced a reaching task with knowledge of results. EG2 practiced the same task with faded knowledge of performance about joint motions	Practiced nonreaching task	60 min/day, 10 days, 2 weeks	1200	Memory, attention, visuospatial ability, executive function	WMSS, RAVLT, ROCF1, CT, WCST, ST, TOL
Ersoy & Iyigun, 2020 <sup>58</sup>	Bobath+VR training (boxing with 4 levels using the Kinect 360 system)	Bobath+real boxing with 4 levels	Bobath: 30 min/day, 3 days/week, 8 weeks (both groups). Interventions (both): 30 min/day, 3 days/week, 8 weeks	1440	Global cognition	ACE-R
Daunoraviciene et al., 2018 <sup>59</sup>	Robot-assisted training (Armeo Spring)	Conventional OT with functional exercises, physical activities, and active table games	30 min/day, 5 days/week, 10 days	1500	Global cognition	ACE-R

Abbreviations: AD, Action Observation; ADLs, activities of daily living; ACE-R, Addenbrooke's Cognitive Assessment-Revised; CT, cancellation test; OT, computerized performance test; EG, experimental group; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; OT, occupational therapy; PT, physical therapy; ROM, range of motion; RAVLT, Rey Auditory Verbal Learning Test; RHB, rehabilitation; ROCF1, Rey-Osterrieth Complex Figure Test; RT, reaction time; ST, Stroop Test; TOL, Tower of London; UL, upper limb; VR, virtual reality; WMSS, Wechsler Memory Scale Stories; WCST, Wisconsin Card Sorting Test.



**Fig 2** Risk of bias of the included studies. **(A)** Risk of bias summary. Authors' judgments broken down for each risk of bias criterion across all included studies. **(B)** Traffic light risk of bias plot. Authors' judgments broken down for each risk of bias domain for every included study.

**Table 3** Results of the methodological quality assessment according to the PEDro scale

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Total
Li et al, 2021 <sup>17</sup>	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	5
Ranzani et al. 2020 <sup>18</sup>	Yes	Yes	No	Yes	No	No	Yes	No	No	Yes	Yes	5
Adomaviciene et al., 2019 <sup>44</sup>	Yes	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4
Shang et al., 2021 <sup>50</sup>	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	5
Taravati et al. 2021 <sup>51</sup>	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	5
Oh et al., 2019 <sup>52</sup>	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	6
Kim & Yim, 2017 <sup>71</sup>	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	6
Choi et al. 2014 <sup>14</sup>	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6
Ozen et al., 2021 <sup>65</sup>	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	6
Wilson et al., 2021 <sup>55</sup>	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	6
Mao et al., 2020 <sup>77</sup>	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7
Lee et al., 2020 <sup>8</sup>	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7
Cirstea, Pito, & Levin, 2006 <sup>19</sup>	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	6
Ersoy & Iyigun, 2020 <sup>60</sup>	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6
Damorauciene et al., 2018 <sup>11</sup>	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	5

NOTE. Item 11 does not count toward the total score.

**Effects of hand motor interventions on global cognition: Bayesian NMA**

**Description of networks**

Eleven studies were included in the Bayesian NMA with effects of 4 possible interventions (supplemental fig S6; available online

only at <http://www.archives-pmr.org/>) on global cognition through MoCA and/or MMSE assessed. Three studies provided effects on both scales. Most studies used conventional RHB as the control intervention (n=10). Three studies compared conventional RHB with conventional RHB + strength training, 4 studies with conventional RHB + robot-assisted training, and 4 studies with conventional RHB + VR training. One study compared 2 robot-assisted

training with VR training both interventions coupled with conventional RHB. Therefore, 4 interventions were compared in the NMA for the variables MoCA ( $n=8$  studies, total number of patients in network=480) and MMSE ( $n=6$  studies, total number of patients in network=350): conventional RHB, strength training, robot-assisted training, and VR training (supplemental table S4; available online only at <http://www.archives-pmr.org/>). The average outcome at post-intervention was 23.94 points for MoCA and 25.43 for MMSE. The number of direct comparisons was largest for the MMSE.

#### Selection of the final model and model assessment

The random-effects model better fitted for MoCA and the fixed-effects for MMSE, both without leverage outliers (supplemental fig S1; available online only at <http://www.archives-pmr.org/>). The consistency model had a better fit than the inconsistency model for both the MoCA and the MMSE (supplemental fig S2; available online only at <http://www.archives-pmr.org/>). When posterior mean deviance of consistency vs inconsistency models were plotted, it showed some discrepancies in the MMSE (supplemental fig S3; available online only at <http://www.archives-pmr.org/>). However, node-split showed no significant differences ( $P>.05$ ) between the direct and indirect comparisons, which reinforced the consistency between studies (supplemental fig S4-A; available online only at <http://www.archives-pmr.org/>). Both the trace plot and the density plot indicated that the number of iterations was sufficient for an adequate convergence of the models (supplemental fig S4-B; available online only at <http://www.archives-pmr.org/>). Meta regression was applied for the MMSE but did not change the degree of discrepancies between the consistency vs inconsistency models and therefore the simpler model without covariables was chosen (supplemental fig S5; available online only at <http://www.archives-pmr.org/>).

#### Ranking of interventions

The interventions with the greatest effect on the MoCA (fig 3A) were strength training (SUCRA=70.42) followed by robot-assisted training (SUCRA=60.08), VR training (SUCRA=53.48), and conventional RHB (SUCRA=16.02). In the MMSE, robot-assisted training (SUCRA=84.41) was followed by strength training (SUCRA=81.86), conventional RHB (SUCRA=29.56), and VR training (SUCRA=4.17). According to the rankogram (fig 3B, supplemental table S7; available online only at <http://www.archives-pmr.org/>), the most probable best intervention for MoCA was strength training (41.68%), followed by robot-assisted training (35.5%), VR training (22.33%), and conventional RHB (0.49%). For MMSE, the most probable best treatment was robot-assisted training (53.61%) followed by strength training (46.39%), conventional RHB (0%), and VR training (0%).

No significant differences were found between any treatment comparisons for MoCA as shown in the league table (fig 4A). For MMSE, there were significant differences between robot-assisted training and conventional RHB [MD=-1.497 (-2.604, -0.396 95% CI)] as well as between robot-assisted training and VR training [MD=-2.16 (-3.164, -1.153 95% CI)], both in favor of robot-assisted interventions (fig 4B). The same was found between strength training and conventional RHB [MD=-1.419 (-2.477, -0.383 95% CI)] and VR training [MD=-2.082 (-3.606, -0.537 95% CI)]. No significant differences were found between robot-assisted and strength training [MD=-0.07 (-1.6, 1.43 95% CI)].

#### Publication bias

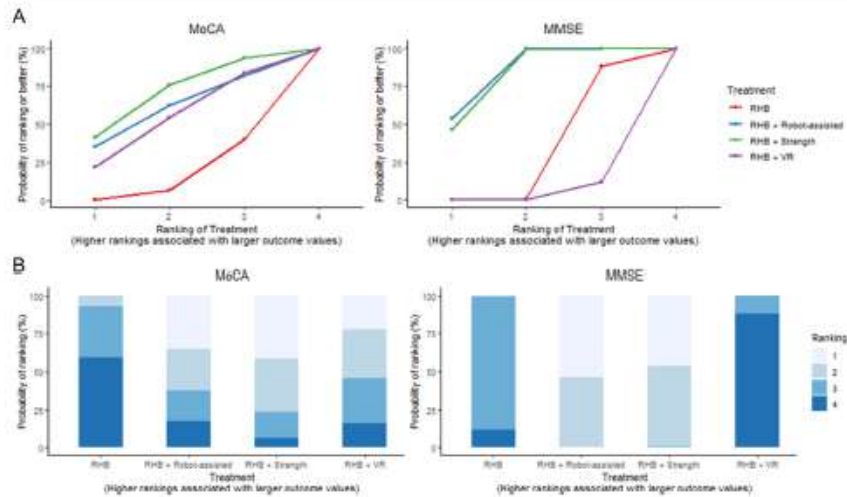
Publication bias was considered negligible ( $D<0.25$ ) assuming different between-study distributions for both the MoCA and MMSE meta-analyses (supplemental table S9; available online only at <http://www.archives-pmr.org/>).

#### Discussion

The present systematic review synthesized the available evidence on the effects of hand motor interventions on cognitive outcomes in individuals with stroke. Fifteen studies were included in the qualitative synthesis and 11 studies in the Bayesian NMA.

Bayesian NMA are becoming increasingly utilized in stroke RHB, for UL motor function and pain,<sup>62</sup> lower limb motor function,<sup>63</sup> dysphagia,<sup>64</sup> or aphasia.<sup>65</sup> The present Bayesian NMA examined the effects of 4 possible physical interventions on global cognition through MoCA and/or MMSE assessments. The results showed that combining strength training or robot-assisted training with conventional RHB had the highest probability of being the most effective intervention for improving global cognition in individuals with stroke, followed by conventional RHB alone or its combination with VR training. However, controversial results were found depending on the outcome measure utilized, as the differences between the interventions were not statistically significant for the MoCA in any of the indirect comparisons, although statistically significant for the MMSE. This may be explained by the fact that although both tests have shown screening validity for post-stroke cognitive impairment,<sup>66</sup> they assess global cognition in non-identical ways.<sup>67</sup> MoCA was developed as a brief tool to screen subjects who present with cognitive complaints and usually have normal MMSE scores, distributing cases across a broader score range with less ceiling effect and greater sensitivity.<sup>68,69</sup> This may have affected on the statistical analysis, as the MoCA network had greater inter-study variability with respect to cognitive status at post-intervention than the MMSE, thus reducing the probability of statistically significant differences to be found. This may explain why the NMA did not yield significant differences between interventions for the MoCA as it did for the MMSE. Overall, the Bayesian NMA was performed with a quite limited number of direct and indirect comparisons available (8 studies in MoCA and 6 studies in MMSE, 4 different interventions each). This is at the boundary for applying this type of statistical analysis, even though the statistical models applied fitted reasonably well with the data and model assessment did not show relevant inconsistencies. However, despite statistical modeling had reasonably well fit, heterogeneity across studies was found regarding participant or intervention characteristics (eg, evolution phase or dosage), which may have affected the results.

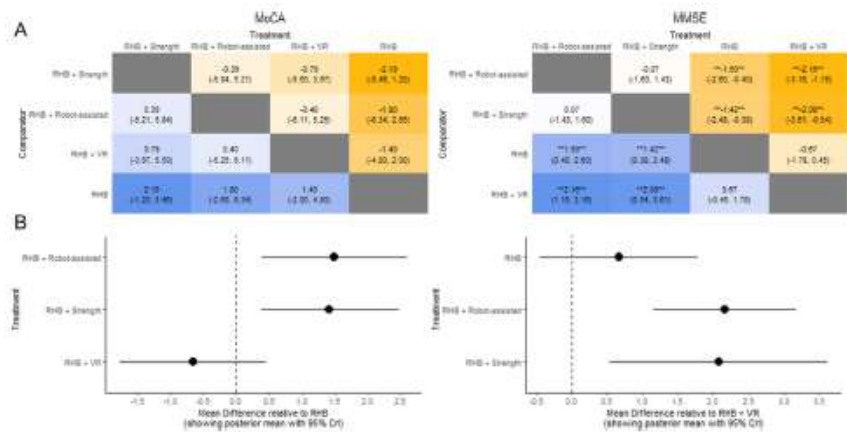
Aside from the above inconsistencies, strength and robot-assisted types of training seemed to be the most effective interventions to enhance global cognition post-stroke. Positive effects of strength training are consistent with a large body of research showing that handgrip training and grip strength are tightly related to global cognition in healthy old adults.<sup>70</sup> Plausible biological mediators of these effects have been studied, for instance, grip force patterns and grip force control may be a direct result of cognitive adaptations during task learning and reflect sensory-motor network changes.<sup>71</sup> In contrast, the relation between robot-assisted training and cognition is less well understood. It may be hypothesized that robot-assisted training is a more comprehensive intervention which combines training of several motor domains,



**Fig 3** Results of network meta-analysis. **(A)** Score of each treatment according to the surface under the cumulative ranking curve (SUCRA) for Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE). **(B)** Rankogram of interventions for MoCA and MMSE. RHB, conventional rehabilitation; VR, virtual reality.

including strength, motor control and synergies, and cross-modal sensory processing thanks to multimodal feedback, as well as indirect training of cognitive domains thanks to the practice of more complex tasks.<sup>72</sup> This would require greater cognitive demands which are trained parallelly with motor components, resulting in a multimodal integration and coordination between sensory-motor and fronto-parietal networks.<sup>73</sup> Conversely, conventional RHB or VR protocols may have lacked these features in the included studies, what may explain why they ranked lower in the NMA.<sup>74</sup>

The qualitative synthesis revealed that most studies found specific cognitive effects of hand motor interventions aside from global cognition, although less studies have been conducted and larger heterogeneity of outcome measures was found. Conventional hand RHB by itself had positive effects on attention, executive control, and information speed processing, what is consistent with a growing body of evidence showing cognitive effects of other RHB schemes such as gait training,<sup>75</sup> resistance training,<sup>26</sup> or general exercise protocols on these domains.<sup>77</sup> Moreover,



**Fig 4** Direct comparison of interventions in network meta-analysis. **(A)** League table of interventions for Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE). **(B)** Forest plots for MMSE. CrI, credible intervals; RHB, conventional rehabilitation; VR, virtual reality.

although the combination of conventional RHB with strength training improved different attention components significantly more than RHB alone,<sup>57</sup> this was only investigated in 1 study. Regarding the use of robot-assisted training, 1 study did not find additional effects on attention measures, whereas another did find statistically significant effects on visuospatial abilities, fluency, and memory domains but not on language or attention and orientation (all measured by the ACE-R). On summary, the cognitive outcomes seemed to be focused on the central executive network, although a lack of formal comprehensive cognitive evaluation did not allow to conclude if there are relevant effects outside of this network. Finally, the combination of conventional RHB with VR training improved attention and executive control, but these effects were not superior to conventional RHB alone.<sup>54</sup> Collectively, these findings reinforce the idea yielded by the NMA on the lack of additional effects of VR paradigms to enhance cognition after stroke, which contrasts with evidence from studies in people with traumatic brain injury.<sup>75</sup> Further research is needed to elucidate the controversial results published so far on the effects of VR training on post-stroke cognition.

Altogether, the results of this systematic review highlight the importance of considering the clinical effects than hand motor interventions may have beyond purely physical aspects. This is in accordance with complementary work demonstrating positive effects of cognitive RHB on motor domains in people with stroke,<sup>76</sup> but also in other neurologic conditions.<sup>80</sup> Therefore, the underlying idea of a cognitive-motor interdependency becomes particularly relevant. From a clinical perspective, our results are congruent with observational studies showing that cognitive and motor domains interrelate in people with stroke.<sup>81</sup> Based on the present systematic review, it is crucial for future research studying the effects of motor interventions post-stroke to consider including at least 1 global cognitive measure in addition to motor outcomes, to advance our understanding of the inter-relations between motor and cognitive recovery.

### Limitations

Some limitations should be noted. First, language biases may have been present, because only studies published in English and Spanish were considered. The diversity of evaluation tools prevented a quantitative synthesis of domain-specific cognitive effects. A limited sample size of comparisons in the NMA impeded performing further analyses using dosage or participant characteristics as covariates. In addition, the NMA might have also been influenced by the limited sample sizes of the studies (8 studies with  $n < 50$  participants and 3 studies with  $n = 50-100$  participants) and the fact that the study of Li et al, 2020 had a total sample of 200 participants. Given this study was included in both the MoCA and MMSE networks, it is likely to have had a significant effect on the results. Regarding participant characteristics, heterogeneous MoCA and MMSE scores at baseline were found across studies, with at least some subgroups of individuals with stroke presenting mild cognitive impairment according to normative cutoffs of these tests, which may impede direct translation of the results into clinical practice. Regarding intervention characteristics, there was high heterogeneity in relation to the content and dosage of some of the interventions, especially for the group analyzed as "conventional RHB". Although all the studies met the criteria to consider they delivered conventional RHB, there was large variability in their protocols, which is a significant limitation and restricts the validity of the NMA findings. Therefore, the findings should be interpreted cautiously. Additionally, lack of reporting of

intervention characteristics in some studies further prevented us from performing meta-regression based on crucial factors such as total dosage or session count. Finally, the small number of studies makes it possible that publication biases cannot be completely ruled out, even though our Robust Bayesian Copas measure indicated they were negligible for both networks.

### Conclusions

Overall, the present study provides evidence that hand motor interventions can improve global cognition in individuals with stroke and possibly focused on fronto-executive functions. Additionally, the results suggest that the combination of strength training or robot-assisted training and conventional RHB may be the most effective intervention for improving cognitive functioning according to MMSE. However, due to the limited number of studies included in this meta-analysis and the heterogeneity across the studies, caution should be taken when interpreting these findings. Further research is needed to confirm these findings across different global cognition outcome measures (including the MMSE, MoCA, or ACE-R) and investigate the effects of hand motor interventions on specific cognitive domains.

### Keywords

Cognition; Hand motor rehabilitation; Rehabilitation; Robot-assisted training; Strength training; Stroke; Virtual reality

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### Acknowledgments

We would like to thank Dr Marcos Ríos for his advice on search strategy design.

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## Appendix H: Paper IEEE Transactions on Neural Systems and Rehabilitation Engineering

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IEEE TRANSACTIONS ON NEURAL SYSTEMS AND REHABILITATION ENGINEERING, VOL. 32, 2024



# AMBER: A Device for Hand Motor and Cognitive Rehabilitation—Development and Proof of Concept

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**Abstract**—Stroke survivors usually exhibit concurrent motor and cognitive impairment. Historically, rehabilitation strategies post-stroke occur separately in terms of motor and cognitive functions. However, recent studies show that hand motor interventions can have a positive impact on cognitive recovery. In this work, we introduce

Manuscript received 18 September 2023; revised 10 April 2024 and 6 June 2024; accepted 12 July 2024. Date of publication 19 July 2024; date of current version 26 July 2024. This work was supported in part by the Spanish Ministry of Science and Innovation under Grant PID2020-113222RB-C21/AEI/10.13039/501100011033. (Corresponding author: Juan Pablo Romero.)

This work involved human subjects or animals in its research. Approval of all ethical and experimental procedures and protocols was granted by CEIM H120 under Application No. 22/495, and performed in line with the 1964 Declaration of Helsinki.

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Digital Object Identifier 10.1109/TNSRE.2024.3429155

AMBER (portAble and Modular device for comprehensive Brain Evaluation and Rehabilitation), a new device developed for the evaluation and rehabilitation of both hand motor function and cognition simultaneously. AMBER is a simple, portable, ergonomic and cheap device based on Force Sensitive Resistors, in which every finger interaction is recorded to provide information about finger strength, processing speed, and memory status. This paper presents the requirements of the device and the design of the system. In addition, a pilot study was conducted with 36 healthy individuals using the evaluation module of the device to assess its psychometric properties, as test-retest reliability and measurement error. Its validity was also evaluated comparing its measurements with three different gold standards for strength, processing speed and memory. The device showed good test-retest reliability for strength (ICC = 0.741-0.852), reaction time (ICC = 0.715 - 0.900) and memory (ICC = 0.556-0.885). These measures were correlated with their corresponding gold standards ( $r = 0.780-0.890$ ). AMBER shows great potential to impact hand rehabilitation, offering therapists a valid, reliable and versatile tool to comprehensively assess patients. With ongoing advancements and refinements, it has the opportunity to significantly impact rehabilitation practices and improve patient outcomes.

**Index Terms**—Hand, upper limb, cognitive status, rehabilitation, robotics, stroke, cognitive evaluation, hand evaluation.

### I. INTRODUCTION

STROKE is one of the leading causes of disability in adults, occurring in around 12.2 million new cases each year [1]. Approximately 80% of stroke survivors suffer from some level of motor impairment in their upper limbs (UL) [2], [3], hindering their ability to perform various activities of daily living (ADLs) over the long term. These alterations frequently affect hand function by provoking hand shaping difficulties, modifying muscle tone or impairing dexterous and fragmented finger movement [4], [5]. Besides motor disability, cognitive impairment is highly prevalent after stroke, with 80% of stroke survivors experiencing deficits in one or more cognitive domains. Attention, short-term memory, and executive function are among the most frequently affected

cognitive abilities [6], [7], [8]. Furthermore, over 20% of survivors exhibit concurrent motor and cognitive impairment in the long term [9]. These two pathological conditions could be correlated, as there are shared underlying neural pathways between motor and cognitive functions, and several studies show an association between motor performance and global cognition, memory and executive function [10], [11], [12], [13], [14].

Several studies have demonstrated a distinct correlation between handgrip strength and a hastened deterioration in overall cognitive performance [15], [16]. Additionally, post-stroke impairments in executive and attention functions have been found to impact the extent of improvement in hand motor function following training [17].

Historically, post-stroke rehabilitation strategies have typically focused separately on motor and cognitive functions [18]. These approaches, often delivered in varying intensities by different professionals, have not fully considered their potential interdependencies [19]. However, there is a growing body of research indicating overlapping effects between them. For instance, hand strength training has been found to have positive effects on cognition in healthy adults [20] and individuals with mild cognitive impairment [21]. Therefore, a comprehensive post-stroke rehabilitation program that incorporates both motor and cognitive aspects is crucial for achieving optimal recovery and the highest possible quality of life [22]. This is specially important during the first 3 months, as it is considered a valuable opportunity window where the own plasticity boosts the recovery of is repeated of strength and motor control after stroke [23], [24].

The paper is structured as follows: Section II provides an explanation of the reviewed literature. Section III outlines the product requirements. Section IV covers various aspects of product development. Section V outlines the evaluation procedure for the proof of concept, while Section VI presents the results of the evaluation. Finally, Section VII delves into the discussion, and Section VIII offers the conclusions.

## II. EXISTING UPPER LIMB REHABILITATION DEVICES

Currently, several devices are used in clinical practice to aid UL motor rehabilitation [25], [26]. Specifically, hand rehabilitation devices are designed to rehabilitate any motor aspect of the hand and to be used in any phase of rehabilitation therapy [26]. Hand rehabilitation devices can be classified into three different categories: orthoses, exoskeletons, or end-effector devices.

Orthoses typically support the hand, protecting it from postures and movements that could cause structural damage. They primarily provide support and alignment for rehabilitation and are commonly low cost, light and easy to use, so the patient can use them from home. However, most of them do not have any actuators or sensors to perform therapy and to be able to track performance data. Examples of hand orthoses used for hand rehabilitation are: Saëbo Stretch [27], Saëbo Flex [28] and Script Orthosis [29].

Exoskeletons, motorized devices designed to enhance physical performance, act on individual finger joints and can be adjusted to fit different hand sizes. They usually have different

sensors to provide a safe and controlled rehabilitation, and a variety of exercises to be used in different phases of rehabilitation. They are also portable, so the patient can use them from home. However, their adjustment and adaptation to each hand require time, the control algorithms are complex, and their costs are usually much higher than orthoses. Exoskeletons can also incorporate gamified environments. Examples of hand exoskeletons are: X-glove [30], HandMate [31], ReHand [32].

End-effector devices tend to be stationary devices with several sensors to provide a high level of control and feedback during motor rehabilitation. They can incorporate higher sensing capabilities and games to engage the patients. However, they are usually complex and expensive, and cannot be portable, so their use is limited to a particular location. Examples of end-effector devices used for hand rehabilitation are: Tyromotion Amadeo [33], HandCare [34], RehaDigit [35].

Crucially, while existing devices enhance motor rehabilitation, the majority are not specifically engineered to simultaneously address cognitive rehabilitation, despite the evidence of indirect benefits to cognitive function [36]. Among the few devices that do explicitly target both domains are HandyKnob and HandyBot, which combine neurocognitive therapy with training and evaluation of motor and sensory functions [37]. However, their use is limited due to their non-portability and the need for specialized supervision. In contrast, AMBER stands out for its portability and ease of use, allowing both the evaluation and rehabilitation of motor and cognitive functions without constant supervision. This feature makes AMBER particularly advantageous for integration into diverse therapeutic environments and could be especially beneficial for home rehabilitation programs, expanding access to comprehensive therapy for patients with mobility restrictions or limited access to specialized centers.

Our goal was to create a small, durable, lightweight, and portable device capable of facilitating the assessment and training of both hand motor function (and individual fingers) and cognition. In this paper, we present the development and initial validation of such a device. Through a proof of concept, we aim to show the system's potential usability, feasibility, and its ability to evaluate a range of motor and cognitive functions. The study involved testing several healthy subjects to assess their hand motor function and general cognitive abilities. The paper offers a comprehensive description of the device's development process and presents the results of the pilot evaluation.

## III. DEVICE REQUIREMENTS AND USE CASES

The primary goal of the device is to facilitate the evaluation and training of both hand motor function and cognitive abilities. To achieve this, the device should possess several key features and capabilities. Firstly, it should be adaptable and ergonomic, capable of adjusting to both right and left hands, adapt to different hand sizes, and allow free movement of each of the fingers separately. Secondly, it should be small, robust, lightweight, and portable, allowing for easy use in various settings, including patients' homes, without the need for additional hardware. Additionally, the device

should feature a user-friendly interface that supports independent operation without the need for continuous clinician oversight. Affordability is also crucial, ensuring the device is cost-effective to manufacture and thus accessible to a wide range of users. In terms of evaluation, the device should incorporate preprogrammed tasks that enable accurate and reliable assessment of hand motor function and cognitive performance, while avoiding physical or mental fatigue that could affect test results. Clinicians should have access to assessment data to track the individual patient progress. By meeting these requirements, the device could effectively serve as a versatile tool for evaluating and rehabilitating hand motor function and cognitive abilities in various clinical settings.

#### IV. PRODUCT DEVELOPMENT

##### A. Hardware

The system architecture proposed in this paper comprises a sensory cylinder and a website designed to function both as a device controller and as a platform for clinicians to access and review evaluation results.

The sensory cylinder, designed for use with either the right or left hand, consists of four individual modules as depicted in Figure 1. Each finger, excluding the thumb, has a dedicated module that can be rotated and adjusted to accommodate different hand sizes and finger lengths. The cylinders are engineered with stops inside, allowing for limited rotation to achieve an adjustable position without causing damage to the inner components of the device. With a height of 24mm, the cylinders provide ample space for finger placement, while their outer diameter of 65mm ensures compatibility with large hands and long fingers without overlapping the thumb when gripped. Moreover, the cylinders are easily graspable by small hands. The structure, designed with a 3D modeling software, is printed using PET (Polyethylene terephthalate) filament, a lightweight, durable, and flexible material, so the structure of the modules is highly resistant to various stresses. Each module features two holes: one small for a colorful light emitter and another larger for a force sensor positioned at the fingerprint area. The inner diameter of the cylinders is designed to accommodate all other electronics and wiring effectively.

The device's electronic system, powered by batteries, includes multiple components for data processing and control. A Raspberry Pi microprocessor serves as the core of the system, along with an analog-to-digital converter (ADC) called ADS1115. Four Force Sensitive Resistor sensors (FSRs) are incorporated to capture data, while four RGB LEDs are included for visual feedback. A power supply ensures the device's operational functionality.

The ADS1115 ADC is responsible for processing the data acquired from the four FSRs, transmitting it to the Raspberry Pi. The Raspberry Pi is equipped with an integrated Wi-Fi module, enabling a connection between the device and a website. This sensory cylinder will receive control signals from the website and transmit the data collected from the sensors back to the website. The utilization of RGB LEDs allows for dynamic color changes, serving different purposes during different operating modes. Furthermore, the device



Fig. 1. The AMBER device. On the left side of the image, the sketch of the layout of the sensory cylinder modules of the device seen from various angles and the 3D layout. On the right side, the device prototype made up with four modules, each with one RGB LED and one FSR.

incorporates a USB-C port input, allowing to be connected to an external power source for charging while in use.

The prototype of the system is lightweight, weighing 252 grams, ensuring its practicality and ease of use.

##### B. Operation Modes

Based on the identified requirements and use cases, the subject's interaction with the device involves engaging with the sensors embedded in each cylinder. The subject will be prompted to press a specific sensor in response to one of the two pre-programmed modes: Evaluation Mode (EM) and Training Mode (TM). Each mode has 3 different exercises. Table 1 shows the explanation of the performance of each exercise, which differ on the feedback (which will be only shown in the EM) and the recorded data (which will be only in the TM).

In the evaluation mode (EM), the device assesses three different aspects: 1) hand and finger strength through grasping repetitions, 2) attention, reaction time, and coordination by having individuals press specific fingers when the corresponding LED lights up, 3) memory evaluation by repeating a previously presented LEDs sequence. The patient's interaction with the device is recorded, and the data is stored and transmitted to a dedicated website.

In the training mode (TM), the tasks are the same three used in the EM but, unlike the EM, the device provides visual feedback to the user in real-time while performing exercises. Different colors indicate the intensity of strength, repetition errors in sequences, or response time to stimuli. Each exercise within the TM offers three difficulty levels.

These exercises were developed using the Python programming language (main packages Adafruit\_ADS1 × 15 and neopixel) and integrated into a HTML website with PHP programming languages and MySQL server for a database, allowing for control and exercise selection for each user through the web-based platform.

The performance of the 3 different exercises is explained in Table 1, where the column "feedback" refers to the exercises on the TM and the column "recorded data" to the EM.

##### C. User Interface

The development of the device includes a website that serves as both a controller for the device and an evaluation

TABLE I  
EXERCISES AND THEIR EXPLANATION

Exercise	Performance	Feedback	Recorded data
Task 1	The user must press the 4 finger FSRs individually or simultaneously at any time	Depending on the amount of force, the corresponding LED emits a colored light, distinguishing 3 grip force ranges: small force: red light; high force: green light; and intermediate force: yellow light.	The device will record the force exerted every 300 milliseconds and the maximum force achieved by each finger in each interaction.
Task 2	The device will emit a sequence of lights while the user must press the button corresponding to each light on as quickly as possible	When the user presses the button, the corresponding light changes its color depending on the reaction speed: the LED will turn green if the user presses the button quickly (in less than 1 second), red if the time is long (more than 2 seconds), and yellow if the time is an intermediate value between the previous established ranges.	The device records the time (in milliseconds) between each light turns on and the corresponding button is pressed.
Task 3	The device will emit a sequence of lights while the user must memorize it and repeat it once it has finished playing	If the button pressed is correct, its corresponding LED will emit green light, if it is wrong, the LED will emit red light.	The device records and check if the buttons pressed are correct, counting the errors, and the force applied in each of them.

platform to access the recorded assessment data. The website, designed in HTML, serves as a controller for the mode of operation and exercises selection and allows each patient to have a private user profile where all their evaluation information (from the EM) is stored.

When logged in, the website first acts as a remote control, enabling users to choose exercises and adjust difficulty levels as desired. Upon turning on the device and login, users (whether clinicians or patients) access the device's website to select the working mode: training or evaluation. In TM, users choose the exercise and desired difficulty level to be executed on the device. Subsequently, the exercise is initiated. In the EM, throughout the exercise, the device records and stores all interactions with the sensors, saving the data in CSV format on the website at the end of each exercise, and displaying them on the web platform. This data can be accessed by clinicians through the web, which provides a simple interface to monitor exercise performance and EM results, and which is accessible remotely. Access to this information is limited to physicians with their own private administrative accounts. The workflow diagram in shown in Figure 2.

## V. EVALUATION PROCEDURE

First of all, the device was subjected to different stress conditions, proving to be structurally resistant and robust. Before testing the device functioning, we performed a focus group with 8 specialists in stroke, each with expertise in different areas (1 neurologist, 2 physiotherapists, 2 occupational therapists, and 1 neuropsychologist). Usability, ergonomics and user requirements were discussed to gather their insights and create the best evaluation protocol for testing the device's performance.

As a first validation of the device, the main purpose was to evaluate the device's reliability as a tool for assessing finger and hand strength and cognitive performance using its EM. Additionally, a correlation between the evaluation results and standardized cognitive and strength assessments was planned.

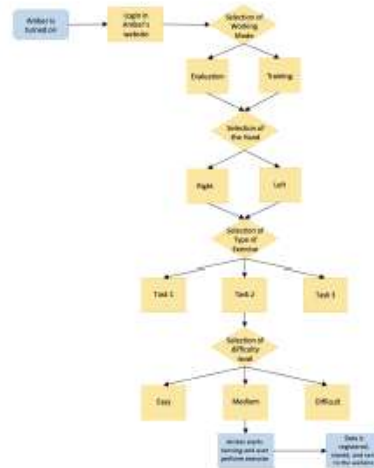


Fig. 2. Workflow diagram of the use of the device and its website.

## A. Study Design

To assess the device's EM, a test-retest reliability and validity study was conducted. The study followed the Guidelines for Reporting Reliability and Agreement Studies (GRRAS) [38]. All procedures were in accordance with the 1964 Declaration of Helsinki and ethical approval was obtained by an independent institutional review board (N° 22/495). All participants gave written informed consent before enrolment.

## B. Participants

Participants were recruited among personnel of the hospital, healthy companions of patients and university students. They were included if they were adults (>18 years) and had neither of the following exclusion criteria: 1) presence of cognitive impairment (Montreal Cognitive Assessment



Fig. 3. Picture of a volunteer grasping and using AMBER device.

(MoCA) < 26 points), 2) known neurological diseases, motor or sensory disturbances that affect hand strength, 3) visual disturbances that prevent visualizing colors such as daltonism or blindness.

Thirty-six healthy individuals participated (19 males), with an average age of  $43.27 \pm 18.52$  years, 31 of them right-handed (assessed through the Edinburgh Handedness Inventory), and with an average MoCA score of  $28.42 \pm 1.66$ .

### C. Assessments

1) *Device Evaluation Mode*: The EM of the device was administered twice to all participants, with at least 3 days apart between sessions to assess test-retest reliability. In each session, the 3 different preprogrammed evaluation tasks described above were administered. As it is intentionally a very simple-to-use device, a relevant learning factor is not expected in any of the tasks.

Task 1 (strength) evaluated finger strength with digits 2, 3, 4, and 5 (which corresponds to the index, middle, ring, and little fingers). The subject was instructed to exert as much force as possible with each finger separately. As in traditional strength assessments, they were verbally encouraged by the examiner not to press any of the other sensors with their remaining fingers to ensure isolated measurements. The average of three attempts per finger (in kilograms) was the outcome measure.

Task 2 (tapping speed) is designed to assess attention and reaction time, and it offers three levels of difficulty: easy, medium, and hard. The user performed each level only once. For this task, the subject was presented with a visual stimulus, where one of the four LEDs corresponding to the four finger sensors would turn on. The subject was then instructed to respond as quick as possible by pressing the sensor corresponding to the illuminated LED using the corresponding finger. The easiest level consists of a sequence involving consecutive fingers. The difficulty increases in the medium and hard levels by introducing more challenging patterns with the omission and repetition of certain fingers. The outcome measure for this task was the average reaction time of the fingers of each hand, and it was recorded in milliseconds.

Task 3 (memory) was designed to evaluate short-term memory at three difficulty levels: easy, medium, and hard. The user performed each level only once with each hand. In this task, the subject was presented with a sequence of LED lights turning on sequentially. The sequence could be of 3, 5, and 7 elements for easy, medium, and hard levels, respectively.

TABLE II  
MEASUREMENTS OF THE FIRST DAY OF EVALUATIONS

Variable	Measurements day 1	
	Mean	SD
<b>Pinch Force – Device (kg)</b>		
Dominant side		
Digit 2	4.76	1.12
Digit 3	3.13	1.19
Digit 4	2.29	1.08
Digit 5	1.37	0.76
Non-dominant side		
Digit 2	3.58	1.25
Digit 3	2.99	1.06
Digit 4	1.92	0.98
Digit 5	1.88	1.16
<b>Pinch Force – Pinch gauge (kg)</b>		
Dominant side		
Digit 2	4.71	1.22
Digit 3	4.10	1.21
Digit 4	3.11	1.15
Digit 5	1.94	0.92
Non-dominant side		
Digit 2	4.32	1.29
Digit 3	4.00	1.29
Digit 4	2.82	1.17
Digit 5	1.97	0.91
<b>TS – Device (msec)</b>		
Dominant side • overall		
Digit 2	695.42	131.86
Digit 3	674.14	111.03
Digit 4	719.83	181.00
Digit 5	704.28	167.00
Digit 5	687.86	172.32
Non-dominant side • overall		
Digit 2	689.03	140.55
Digit 3	627.97	145.18
Digit 4	668.42	185.10
Digit 5	695.75	110.17
Digit 5	762.72	171.40
<b>TS – computerized (msec)</b>		
Tapping speed		
Dominant side	164.85	24.11
Non-dominant side	185.21	31.25
Mean sides	173.93	26.50
Simple reaction time	281.89	30.46
<b>Memory – Device</b>		
Score	3.83	1.34
<b>Memory – Digits-D WAIS-IV</b>		
Score	4.53	1.11
<b>Memory – CBT</b>		
Score	4.47	1.16

SD, standard deviation; kg, kilograms; TS, Tapping Speed; msec, milliseconds; Digits-D WAIS-IV, Direct version of the Digit Test from Wechsler Adult Intelligence Scale-IV; CBT, Corsi Block-Tapping Test

Once the sequence was completed, the subject was asked to recall the sequence pressing the sensors corresponding to each finger in the correct order. Participants were explicitly indicated that there were no time constraints to respond to this task, and they had to prioritize accuracy over speed. The outcome measure for this task was the number of completely correct sequences recalled by the subject.

All tasks were performed first with the dominant hand and then with the non-dominant hand.

2) *Comparison With Conventional Finger Pinch Force Evaluation*: The pinch force assessment was administered once to all participants, the same day as the first evaluation with the device. All participants were instructed to sit on a chair approximately 60 cm ahead of the computer monitor.

According to the guidelines from the American Society of Hand Therapists, the participants were supposed to have a vertical positioning of the upper arm, a 90° -flex of the elbow, and neutral positions of the wrist and forearm [39]. The pinch force was placed over the device in a position that allowed the “pinch force sensor” to interact with the examined finger against the device during the full hand grip. Subjects were asked to produce as much force as possible with each finger using thumb pad to the evaluated finger pad pinch during 3 seconds separately with an analog baseline hydraulic pinch gauge (MVS in motion, Belgium) [40], in an analogous way as it was done with the device's sensors. The average of the kilograms of force of three attempts per finger was the outcome measure. This was performed first with each finger of the dominant hand, and then with the fingers of the non-dominant hand.

3) *Comparison With Standardized Evaluation of Cognitive Variables:* Processing speed and tapping speed evaluation was carried out through different computerized tasks controlled by Presentation® software (<http://www.neurobs.com>) as described elsewhere [41]. The first task was the Finger Tapping (FT), used as a measure of motor speed, providing quantitative information on slowing down of responses [42], [43], [44]. In this task, following the Strauss application norms [44], the participants were instructed to press the spacebar on the keyboard as fast as possible and repeatedly with the index finger (digit 2). Five 10-s attempts with each hand were performed. The average of response times (in milliseconds) recorded between 2 consecutive taps was the outcome measure of this first task. The second task, simple reaction time, is inspired by the SRT task of the Computerized Information Processing Testing battery [45]. This task was used as a measure of information processing speed [46]. It is the time elapsed between the presentation of a stimulus and the execution of a motor response [47]. Participants were instructed to press the left mouse button as fast as possible when the “+” stimulus appeared in the center of the screen at varying inter-stimulus times. Only the dominant hand was used for this task. The average time between the appearance of the stimulus and the motor response was the outcome measure in this task.

Immediate and working memory, as well as phonological learning, were assessed using the direct version of the digit test of the Wechsler Adult Intelligence Scale-IV (WAIS-IV) [48], [49], where the subject, after hearing a sequence of numbers from the examiner, had to memorize and immediately repeat the sequence out loud trying to avoid errors. The number of completely correct sequences was the outcome measure. Spatial and visual memory was tested through the Forward version of the Corsi Block-Tapping Test (CBT) [50], where the subject had to memorize and tap a sequence of blocks displayed on a table in the same order that the examiner had previously tapped on a subset of nine blocks. The number of completely correct sequences was the outcome measure.

#### D. Usability Study

After both evaluations, a usability study was also carried out, asking all volunteers to answer a questionnaire where

different questions were asked about the comfort and ease of use of the device. The questions were as follows: How easy (comfortable) was it for you to hold the device with your dominant hand? How easy (comfortable) was it to hold the device with your non-dominant hand? How complex was it for you to understand how the exercises work? Did the sensors on each finger seem to sensitively reflect the force you exerted (task 1)? How difficult were the tapping speed exercises (task 2) for you? How difficult were the memory exercises (task 3) for you? All questions were scored from 0 to 10, with 0 being the lowest score and 10 being the highest score. Finally, the volunteers were asked if they would recommend the use of this device to a family member with brain damage.

#### E. Statistical Analysis

Statistical analyses were performed using SPSS v 25.0 software (IBM Corp. Armond, NY). Specifically, the test-retest reliability of the device was analyzed to assess the stability of the measurements over time. This analysis was carried out through the Intraclass Correlation Coefficient (ICC) with a two-factor mixed model of average measures and consistency agreement. 95% confidence intervals of the ICC were obtained for measures of Tasks 1-3. ICCs were interpreted as <0.5, 0.5-0.75, 0.75-0.9 and >0.9 for poor, moderate, good, excellent reliability, respectively [51]. Additionally, limits of agreement were obtained by means of Bland-Altman plots, computing the difference between test and retest against the mean of the two measurements [52]. Standard Error of Measurement (SEM) was also obtained following the formula  $SEM = SD * \sqrt{1-ICC}$  [53]. Test-retest reliability analysis was performed after removing outlier observations in which, for the same type of measurement of a specific subject, the test and retest values differed by more than 100%.

Construct validity was analyzed to assess the accuracy with which the device measures each construct in Tasks 1-3 against the standardized assessments used as gold standards. This was done through the Pearson correlation coefficient. Pearson's  $r$  was interpreted as showing negligible, weak, moderate, strong or very strong correlation for values 0.00-0.09, 0.10-0.39, 0.40-0.69, 0.70-0.89, 0.90-1.00, respectively [54]. For this analysis,  $\alpha = 0.05$  was set for statistical significance.

### VI. EVALUATION RESULTS

Thirty-six participants initially enrolled in the study between February and May 2023 and completed both assessment sessions, with a mean interval of  $6 \pm 1.89$  days between test and retest. Missing data for at least one task and session were present in 4 participants. The main results are shown in Table III.

#### A. Test-Retest Reliability

Reliability and SEM results for each Task and finger, are shown in Table III. In Task 1 (strength),  $ICC = 0.741-0.852$  showed moderate to good test-retest reliability. The device was slightly more reliable with the non-dominant than the dominant hand ( $ICC = 0.784-0.852$  vs  $ICC = 0.741-0.801$ , respectively). Accordingly, SEM was higher for the

TABLE III  
RELIABILITY RESULTS OF VARIABLES MEASURED BY THE DEVICE

Variable	Device Test (day 1)		Device Retest (day 2)		ICC (95% CI)	SEM
	Mean	SD	Mean	SD		
<b>Task 1 – Strength (kg)</b>						
Dominant side						
Digit 2 (N=32)	4.76	1.12	3.97	1.52	0.741 (0.470-0.874)	0.570
Digit 3 (N=36)	3.13	1.19	3.13	1.25	0.801 (0.611-0.899)	0.531
Digit 4 (N=34)	2.29	1.08	2.07	1.08	0.786 (0.572-0.893)	0.500
Digit 5 (N=33)	1.37	0.76	1.24	0.67	0.784 (0.562-0.893)	0.353
Non-dominant side						
Digit 2 (N=35)	3.58	1.25	3.15	1.43	0.851 (0.704-0.925)	0.483
Digit 3 (N=35)	2.99	1.06	2.73	1.38	0.784 (0.572-0.891)	0.493
Digit 4 (N=35)	1.92	0.98	1.89	1.25	0.852 (0.707-0.925)	0.377
Digit 5 (N=32)	1.88	1.16	1.53	1.06	0.814 (0.619-0.909)	0.500
<b>Task 2 – TS (msec), N=35</b>						
Average of levels						
Dominant side (overall)	695.42	131.86	615.08	123.54	0.782 (0.568-0.890)	61.57
Non-dominant side (overall)	689.63	140.55	657.00	136.19	0.833 (0.668-0.916)	57.44
Easy Level						
Dominant side (overall)	679.39	170.43	627.76	128.54	0.707 (0.420-0.852)	92.253
Non-dominant side (overall)	669.59	177.55	630.50	171.21	0.684 (0.373-0.840)	99.808
Medium Level						
Dominant side (overall)	661.17	100.99	623.10	127.13	0.805 (0.610-0.903)	44.596
Non-dominant side (overall)	686.97	161.49	659.59	137.94	0.718 (0.442-0.858)	85.757
Hard Level						
Dominant side (overall)	756.36	130.00	657.22	126.53	0.696 (0.392-0.848)	71.677
Non-dominant side (overall)	725.90	175.38	686.96	130.78	0.554 (0.107-0.777)	117.124
<b>Task 3 – Memory (number of right answers), N=36</b>						
Score	3.83	1.34	4.53	1.23	0.774 (0.556-0.885)	0.637

Note: Different sample sizes correspond to the actual number of participants analyzed after removing observations that were statistical outliers (i.e. if the test and retest values differed by more than 100%, being considered execution or measurement errors). Abbreviations: SD, standard deviation; kg, kilograms; TS, Tapping Speed; msec, milliseconds; ICC, Intraclass Correlation Coefficient; CI, confidence interval; SEM, standard error of measurement.

dominant hand compared to the non-dominant side (SEM = 0.353-0.570 kg vs SEM = 0.377-0.500 kg, respectively).

In Task 2 (tapping speed), ICC = 0.715 – 0.90 showed moderate to good test-retest reliability. In this case, the device was also slightly more reliable with the non-dominant than the dominant hand (ICC = 0.74-0.90 vs ICC = 0.715-0.863, respectively). Accordingly, SEM was higher for the dominant hand compared to the non-dominant side (SEM = 0.059-0.090 sec vs SEM = 0.037-0.094 kg, respectively). It is also important to highlight the significant difference between levels. Specifically, this difference takes place between the medium and difficult levels on the dominant side: Mean Difference = -93.96 milliseconds 95% CI [-146.40, -41.32],  $t(34) = -3.63$ ,  $p = 0.001$ .

In Task 3 (memory), ICC = 0.774 showed good test-retest reliability.

### B. Construct Validity

Correlation analysis between each Task and conventional evaluation of finger pinch force and cognitive variables are shown in Table IV and Table V.

In Task 1 (strength), the device showed moderate to strong correlations with its pinch force counterparts ( $\rho = 0.563-0.781$ , all  $p < 0.001$ ). Comparable correlations between the device and pinch force were found across fingers in each hand, and in finger pairs (i.e., index-index) across hands.

In Task 2 (tapping speed), correlations with computerized finger tapping were higher as the difficulty of the exercise

TABLE IV  
CORRELATION RESULTS OF THE FORCE MEASURED BY THE DEVICE AND THE PINCH GAUGE

Device	Pinch gauge	
	Pearson's $r$	P-value
Dominant side		
Digit 2	0.766	< 0.001
Digit 3	0.597	< 0.001
Digit 4	0.563	0.001
Digit 5	0.671	< 0.001
Non-dominant side		
Digit 2	0.781	< 0.001
Digit 3	0.648	< 0.001
Digit 4	0.744	< 0.001
Digit 5	0.756	< 0.001

increased ( $\rho = 0.383-0.702$ , all  $p < 0.05$ ). Comparable correlations were found between the device and simple reaction time task, higher correlations were seen comparing the hardest level of the device and also comparing the average value of all the 3 difficulty levels for both hands with the computerized task.

In Task 3 (memory), the device showed moderate correlations with the direct version of the Digit test from WAIS-IV ( $\rho = 0.637$ ,  $p < 0.001$ ). To calculate this correlation, since the memory exercise of the device has 3 levels of difficulty with memorization of sequences of 3, 5 and 7 digits, we used a subscore of the Digits test, comprising only the sequences of 3, 5 and 7 digits among all those in the test. On the other hand, the Task 3 of the device showed a weak correlation with

**TABLE V**  
CORRELATION RESULTS OF THE REACTION TIME MEASURED BY THE DEVICE AND COMPUTERIZED TAPPING SPEED AND DEVICE TASKS

Variable	Tapping		Simple reaction time	
	Pearson's <i>r</i>	P-value	Pearson's <i>r</i>	P-value
<b>Average of levels</b>				
Dominant side*	0.592	< 0.001	0.373	0.025
Non-dominant side*	0.649	< 0.001	-	-
<b>Easy level</b>				
Dominant side*	0.383	0.021	0.138	0.422
Non-dominant side*	0.444	0.007	-	-
<b>Medium level</b>				
Dominant side*	0.447	0.006	0.334	0.006
Non-dominant side*	0.426	0.010	-	-
<b>Hard level</b>				
Dominant side*	0.592	< 0.001	0.422	< 0.001
Non-dominant side*	0.702	< 0.001	-	-

\* Overall value calculated as the mean of the values of all fingers of each side.

the forward version of the CBT, which was not statistically significant ( $\rho = 0.236$ ,  $p = 0.116$ ).

### C. Usability Test With Healthy Subjects

A usability test was carried out through a questionnaire on the healthy volunteers who participated in the validation study, with the aim of knowing how complex the use of the device had been for them and whether they found it responsive to its interaction. Through different questions, we saw that 90.9% of the volunteers found the device easy or very easy to grab while using it with their dominant hand. While with the non-dominant hand the percentage decreased to 54.5%, with 4.5% of them finding it difficult to grasp. Regarding understanding the functioning of the device, 95.4% found it easy or very easy to understand how the device and its exercises work. About the difficulty on the performance of the exercises, 31.8% of the users did not find the reaction speed exercises (task 2) difficult at all, while the remaining 68.2% found them easy. With respect to the memory exercises (task 3), 9.1% found them quite difficult, 72.7% found them somewhat difficult, and the remaining 9.1% found them easy. Furthermore, all participants thought that the device was reasonably accurate with respect to the force they were doing. Finally, 81.8% stated with certainty that they would recommend the use of this device to a family member with stroke, and no volunteer rejected it.

## VII. DISCUSSION

An extensive review of the literature on current technological devices for diagnosing and treating hand and cognitive functions reveals that almost none of them are designed to simultaneously train both skills. This finding underscores the importance of developing and utilizing a device that integrates both dimensions [26], [31], [33], [34], [37]. Moreover, the majority of existing devices lack the capability for continuous data recording and storage, crucial for monitoring user progress and status. Often, these devices are often large, heavy, expensive, and difficult to use, restricting their accessibility to many patients. This issue is particularly relevant among stroke patients, who frequently cannot resume daily activities and

become reliant on caregivers. Furthermore, in rural areas or during difficult health situations, such as the recent Covid-19 pandemic, accessing a hospital for rehabilitation sessions can be a significant challenge.

Among the few devices that do explicitly target both domains are HandyKnob and HandyBot, which combine neurocognitive therapy with training and evaluation of motor and sensory functions [24], [37]. However, their use is limited due to their non-portability and the need for specialized supervision. In contrast, AMBER stands out for its portability and ease of use, allowing both the evaluation and rehabilitation of motor and cognitive functions with the use of pre-programmed tasks. This feature makes AMBER particularly advantageous for integration into diverse therapeutic environments and could be especially beneficial for home rehabilitation programs, expanding access to comprehensive therapy for patients with mobility restrictions or limited access to specialized centers.

Therefore, this paper aims to introduce the development of a novel device designed for assessing and training fingers motor functions and cognitive features in a portable, easy and gamifying procedure, and validating the precision and reliability of the evaluation mode of such a device.

Targeted at individuals with neurological impairments, particularly stroke, the device underwent a comprehensive evaluation process in line with the specified requirements, taking into consideration its intended application, human factors as handedness, and potential future clinical use.

The device demonstrates technical capabilities that allow the desired assessments to be performed with minimal measurement error. Furthermore, the precision of its EM was thoroughly assessed. It can measure the precise force performed with each finger and is able to provide an assessment of several cognitive functions that could be used to evaluate processing speed, attention and memory. Test-retest reliability for the three measurements (strength, reaction time and memory) shows moderate to good results. The results of this preliminary study conducted with healthy subjects are presented and discussed in the following subsections.

### A. Strength

Strength measures show moderate to good reliability, comparable to the available gold standard (i.e. pinch force) [55]. In our study, the digit 2 (index) of the dominant hand was the finger with lower reliability values. The reason behind this lower reliability is likely attributed to the notably higher strength values recorded for the dominant hand's digit 2 on the first day compared to the second day. This discrepancy is possibly due to the testing protocol, where all evaluations began with the digit 2 first, followed sequentially by the other fingers, without providing the option of a first familiarization trial. The subjects, when confronted with this new device, might have felt uncomfortable during their initial grip of the device with their digit 2. This discomfort may have been the reason they did not exert force in the same way on both days. However, as they progressed to the second day, familiarity with the grip of the device and the specific way they needed to press each finger may have led to more consistent strength measurements for the digit 2.

Regarding the correlation between fingers strength measured by the device and its "gold standard", the pinch gauge, there is a moderate to good correlation.

### B. Processing Speed (Tapping Speed)

In terms of the reliability of reaction times, there is a moderate to good correlation between the test and retest results. To calculate this correlation, the reaction times of each finger at each difficulty level were averaged.

Reaction time is a measure of how quickly the brain processes information and responds to it. It includes the time it takes to detect a stimulus and the time it takes to produce a motor response. In between, there are complex cognitive processes that happen in a graded manner.

The simplest task is the finger tapping task, where no cognitive processing is involved. This task allows us to directly evaluate motor skills, the reliability on the execution of this task rules out the influence of motor components in cognitive processing. The second task of our device, although it is the simpler reaction time, is a more complex task, participants need to detect a stimulus and respond to it while sensory and motor components interact. Additionally, the response is done with just one finger while inhibiting the rest, thus not only attention but also inhibitory control is expected to be involved.

For the analysis of the results of the assessment with the device, the finger that executed the response is not differentiated. This is because the different motor control capabilities of each finger cannot be controlled, as they largely depend on individual differences between participants.

Among the three levels of difficulty, the medium level demonstrates the highest reliability ( $ICC = 0.805$  with the dominant hand and  $ICC = 0.718$  with the non-dominant hand). While one might assume that the reliability would decrease as the level of difficulty increases, in this case, the easiest level actually exhibits lower reliability than the medium level. This could be attributed to the fact that subjects didn't undergo any training trial, and the easy level helps them understand the exercise dynamics better.

Regarding the hardest level, the lower reliability could be due to a greater increase in difficulty than intended, leading subjects to face a more challenging task compared to the transition from the first level to the second. Furthermore, at all difficulty levels, a decrease in reaction time is observed during the retest compared to the initial test. This suggests that subjects become more familiar with the exercises during the first assessment.

Regarding the correlation with the computerized evaluation of reaction times, it is worth specifying the two reaction time constructs used: Tapping, which is a simple motor task with no cognitive processing involved, and simple reaction time, a more complex cognitive task involving sensory and motor elements. It was only evaluated the simple reaction time construct using the dominant hand, as assessing the non-dominant hand could introduce unexpected motor variables due to the ease of using the computer mouse.

Overall, a significant positive correlations between the device's measurements and both tapping and simple reaction

times is observed. On the dominant side, the device's measurements show a moderately strong correlation with tapping (Pearson's  $r$  range: 0.383 to 0.592) and a relatively weaker correlation with simple reaction time (Pearson's  $r$  range: 0.138 to 0.422). These correlations are statistically significant for all difficulty levels.

On the non-dominant side, it is also observed significant positive correlations between the device's measurements and tapping (Pearson's  $r$  range: 0.426 to 0.702).

Regarding the different levels of difficulty, the correlations remain consistent with the overall trend. At the easy level, the device's measurements exhibit a moderate correlation with tapping on both dominant and non-dominant sides. However, for the simple reaction time task, the correlations are weaker and non-significant, which suggests that the device's measurements might be more reflective of simple motor tasks rather than cognitive tasks involving perception at this level.

Moving to the medium level, the correlations between the device's measurements and tapping are moderate and statistically significant on both dominant and non-dominant sides. The same occurs for the simple reaction time task. The strength of the correlations increases compared to the easy level, indicating that the device's measurements captured variations in both simple motor tasks and simple reaction time tasks more effectively at this level.

At the hard level, the correlations between the device's measurements and tapping on both sides are strong and statistically significant. The correlation with the simple reaction time task are also better than at the moderate level.

In summary, the results suggest that our device's capability to measure reaction times is positively correlated with both tapping (simple motor task) and simple reaction time (more complex cognitive task) across different difficulty levels. The device appears to be more sensitive to simple motor tasks' reaction time overall and shows stronger correlations compared to tasks requiring cognitive involvement as perception, especially at easier levels. These findings may reflect that the response to easiest levels is done in an automatic manner, similarly to the tapping paradigm in computerized evaluation, as the cadence of appearance of the stimulus is constant, so the activation of complex cognitive processes is not needed. The poorer correlation might be justified by the fact that the stimulus presentation in the computerized simple reaction task is variable, whereas in our device, it is done at a regular frequency, just varying the location of the stimuli.

### C. Memory

Finally, evaluating memory exercise shows good reliability and demonstrates a strong positive correlation when compared to conventional evaluations as a subscore of the direct version of the Digit test from WAIS-IV, despite the auditory learning paradigm used in that test. Our device utilizes different stimulus locations that need to be memorized, leading us to also employ the forward version of the Corsi Block-Tapping Test (CBT) for comparison. However, the correlation with CBT was not statistically significant ( $\rho = 0.236$ ,  $p = 0.116$ ). This lack of significance may be attributed to the fact that fingers are often associated with numerical symbols, and their memorization

might be following the phonologic learning pathway, similar to the digits test, rather than the CBT [56].

#### D. Limitations and Future Development

During the evaluations, several limitations of the device were identified. First, the device's operation has a drawback in terms of battery capacity. The limited battery charge may restrict its extensive use, often necessitating connection to a power source for prolonged usage. This could be addressed by incorporating higher capacity batteries to enhance its usability. Another limitation is the absence of a specific sensor for the thumb (digit 1). Since many daily activities heavily rely on the use of this finger, its exclusion may limit the device's full potential in interactions with users. Moreover, the fact that the patient must hold the device could be a challenge, particularly for those with impairments or limited abduction capabilities. Survey feedback from healthy subjects highlights this issue; specifically, 46% of participants reported difficulties in gripping and using the device effectively with their non-dominant hand, which they described as their less skilled hand. This may be because of the high demand for motor and cognitive control required to operate the cylinder with a flexed wrist to see the LED indicators. To address this, the design of a wrist strap or a table support will be considered, allowing the device to be used while supported. Future changes in light positions, so they can be seen without flexing the wrist, may also help reduce the difficulty. However, it should always be noted that this device is intended as a complementary tool to other techniques and devices, and may not be appropriate for all users. Regarding the tasks, Task 2 has a potential for improvement making it more close to computerized finger tapping test by incorporating a simple motor task, such as repeatedly pressing one sensor as fast as possible. Additionally, introducing more variability in the sequences of the LED signals during the evaluation of reaction times may enable a more complex assessment and yield a stronger correlation with computerized tasks. Task 3 could be enhanced by including more sequence levels to make it more similar to the Direct Digits task. Even the possibility of programming an inverse sequence, after the inverse digits test in WAIS-IV evaluation, could facilitate a more comprehensive evaluation of memory function. Regarding the assessment procedure, the lack of a counterbalanced order for the first finger to be tested is a limitation, as a random assignment to finger order would have been desirable. Finally, a calibration of the tasks according to each subject's abilities would be very useful to be used more easily and widely by different profiles of patients.

Addressing these limitations would lead to an improved and more versatile device, broadening its potential applications and increasing its overall utility in various clinical and research settings. Since this article and study is a proof of concept and validation with healthy subjects, subsequent studies such as a clinical trial to test the effectiveness of the TM, in stroke populations, are needed in the future. This will serve to validate its usefulness as a therapeutic tool.

#### VIII. CONCLUSION

The uniqueness of this device lies in its ergonomic design, adaptability, robustness, and reliability as a comprehensive tool for measuring force, memory, attention and coordination. AMBER holds great promise as a valuable tool for therapists, enabling them to conduct reliable evaluations and potentially address motor and cognitive variables in patients using a single, portable, and cost-effective device. It has the potential to offer flexible programming and establish stronger correlations with more complex cognitive evaluations. In comparison to other hand rehabilitation devices, AMBER goes beyond them by incorporating cognitive rehabilitation tasks, a feature absent in existing devices.

#### ACKNOWLEDGMENT

The authors would like to thank María Teresa Bocanera, Jesús Rodríguez Herranz, and Guillermo Catalán Sarrié for their advice during the completion of this study.

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