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The role of clinical neuropsychology in neuromotor rehabilitation

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“La prima medicina, l’infinito amore”

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ABSTRACT

Background. Stroke and multiple sclerosis (MS) are chronic disability condition, comprising motor, cognitive and psychological deficit, thus a poor health-related quality of life (HRQoL). Through a multidisciplinary biopsychosocial approach, the focus of the present work is to explore the potential benefits of plasticity-based technologies and interventions in a clinical rehabilitation setting. The aim of this thesis is to evaluate the influence of cognitive functioning in neuromotor rehabilitation.

Methods. In this thesis, I present five studies of patient with physical disability, MS and Stroke; precisely, two randomized clinical trial, one study protocol and two observational studies. The method of each study is resume below.

1. MS patients (n=16) was randomly assigned to receive real- or sham- cerebellar transcranial direct current stimulation (ctDCS) and Task-Oriented Circuit Training daily over two weeks. Functional mobility, balance, walking performance, quality of life, psychological and executive functioning were tested before and after treatment and at 2-weeks follow-up.
2. MS patients (n=48) will be randomly assigned to receive three sessions/week for 1 months of either Video Game Therapy (VGT) or Balance Platform Training (BPT). Outcome measure comprehends functional mobility, stability, gait, risk of fall, fatigue and health-related quality of life as well as cognitive and psychological aspects. These were tested before and after the training and at 3 months follow-up.
3. Subacute stroke patients (n=12) underwent Action Observation Training (AOT) 5 days/week, for 1 month. Patients were divided into two subgroups: with/without attention deficit based on the neuropsychological evaluation. The accuracy of interactive computerized exercises was used as a measure of concentration during the training, and a questionnaire was used to measure patients' engagement.
4. Stroke survivors (n=39) were assessed using the Stroke Impact Scale before, after three weeks, at the end of rehabilitation (6-week), after 6-months and six years. SIS domain scores were calculated over time in relation to age, sex and stroke severity. Long-term changes were explored through clinically meaningful changes of SIS-16 (physical SIS).
5. Adult patients with physical disabilities (n=23) carried out a telerehabilitation program during the COVID-19 pandemic. The feasibility and acceptability and the barriers and facilitators to the adoption of telerehabilitation, were identified. Clinical, demographic, and psychological variables were analysed as predictors of success.

Results. According with the previous numbering, the results of each study are detailed below.

1. Task-Oriented Circuit Training in MS effectively ameliorated balance, mobility and executive functioning, but cerebellar tDCS did not boost training effects. Anxiety/depression did not show significant changes, although patients perceived a better mental HRQoL after treatment.
2. From the study, it is expectancy to detect a more significant effect on mobility, balance and dual-task through VGT, besides an improvement in the psychological component.
3. All stroke patients improved motor function; however, attention deficit, stroke severity and anxiety/depression are significant predictor for increment of sensorimotor functioning. Patients with attention deficit described a lower level of engagement and a lower mean accuracy of interactive computerized exercises used to maintain concentration during the training. With regards to accuracy, trends showed sustained improvement up to the 3° week and then decayed – perhaps due to a decrease in involvement of the training.
4. Through the Stroke Impact Scale, it was showed that Disability and HR-QoL improved after rehabilitation independently of type treatment, but deteriorated 6 years after stroke, except for Memory and Thinking Ability, Emotions and Communication domains. Stroke severity, male gender and older age are all factors that influenced total score. Baseline SIS-16 (only physical domains), presence of a sensory deficit and patient's setting were factors related to SIS-16 at the end of rehabilitation and after 6 months.
5. Patients with physical disabilities show a good level of feasibility and acceptability of telerehabilitation program, despite some technology challenges and preference traditional in-

person treatment. Age, cognitive reserve, and resilience were significant predictors of satisfaction with telerehabilitation.

Discussion. These studies confirm that the presence of cognitive or mood disorder besides influencing each other’s may greatly impact the process of rehabilitation and its final outcome. Some limitations that regards not only the small sample size and lack of quantitative neurophysiological data are present. The studies were carried out also during the pandemic, involving organizational difficulties, as well as being a confounding factor of data collected.

Conclusion. This thesis highlights the relation between cognitive and motor processes and raise several practical implications for designing effective rehabilitation programs, that impact also in mood and HRQOL; hence the importance of the role of the neuropsychologist in the neurorehabilitation setting. Among the future perspective is to design studies that quantify cognitive functioning as their primary outcome.

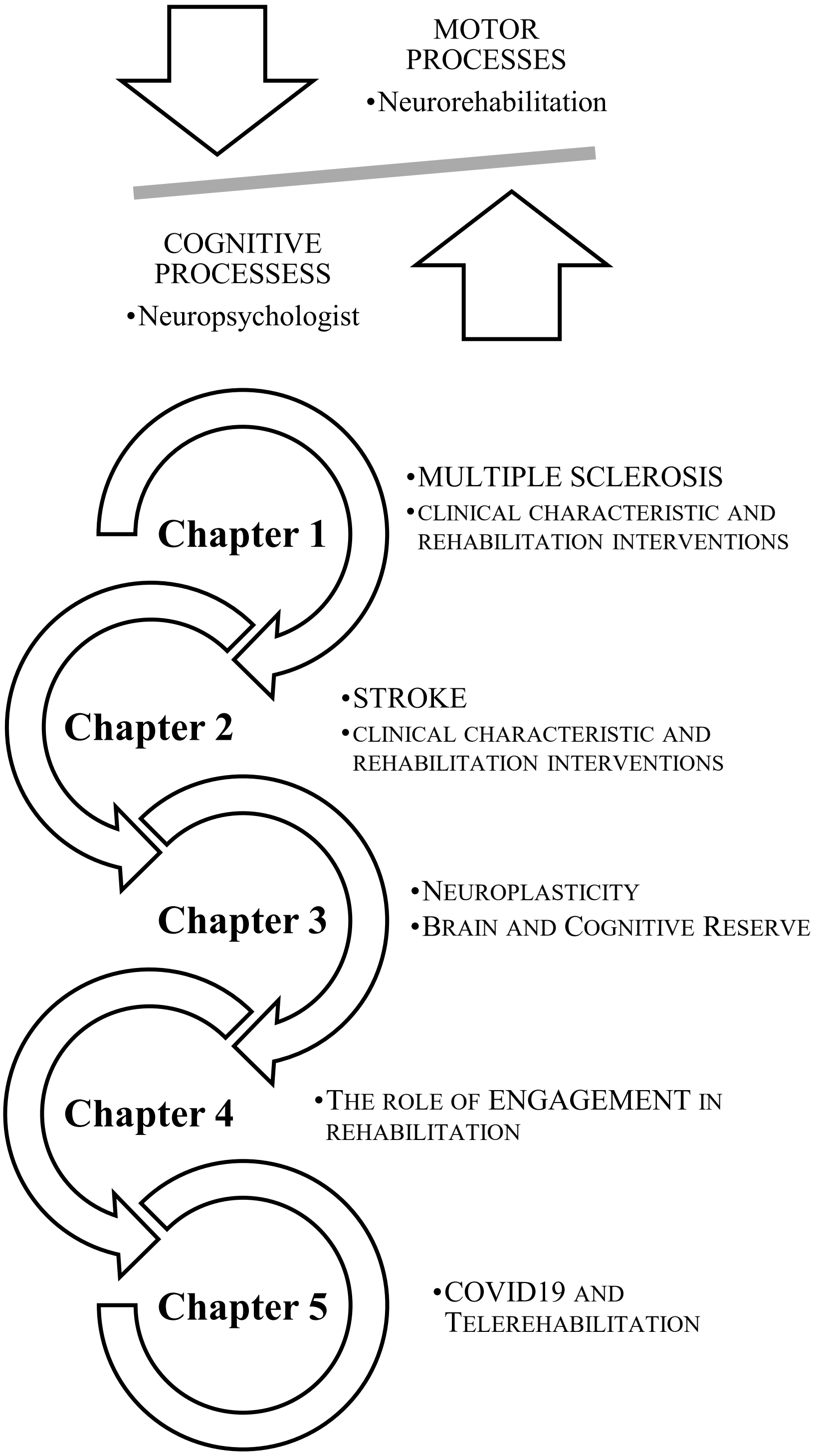
Keywords: Multiple Sclerosis, Stroke, Neuropsychology, Neuro-Rehabilitation, Engagement, Quality Of Life

ABBREVIATIONS

RAT	Robot-assisted therapy
FES	Functional electrical stimulation
ICT	Intensive conventional therapy
BI	Barthel Index
FMA	Fugl-Meyer Motor Assessment
WMFT	Wolf Motor Function Test
MAS	Modified Ashworth Scale
TMS	Transcranial magnetic stimulation
MEPs	Motor-evoked potentials
SIS	Stroke Impact Scale
PwMS	People with multiple sclerosis
TOCT	Task-oriented circuit training
tDCS	Transcranial direct current stimulation
CBI	Cerebellum-brain inhibition
ctDCS	Cerebellar transcranial direct current stimulation
COVID-19	Severe Acute Respiratory Syndrome - Coronavirus – 2
SUS	System Usability Scale
TFS	Technology Familiarity Scale
CRIq	Cognitive Reserve Index questionnaire
GSE	General Self-Efficacy Scale
CD-RISC	Connor and Davidson Resilience Scale
SF-12	12-Item Short Form Survey
PHQ-9	Patient Health Questionnaire
BAI	Beck Anxiety Inventory
MS	Multiple sclerosis
VGT	Video game therapy
BPT	Balance platform training
CNS	Central nervous system
DGI	Dynamic Gait Index
FSST	Four Square Step Test
FRT	Functional Reach Test
MSIS-29	Multiple Sclerosis Impact Scale—29
MSWS-12	Multiple Sclerosis Walking Scale—12
MFIS	Modified Fatigue Impact Scale
BDI-II	Beck Depression Inventory—Second Edition
STAI-Y	State Trait Anxiety Inventory
T.A.P.	Test of Attentional Performance
SCWT	Stroop Color-Word Test
SDMT	Symbol Digit Modalities Test
AOT	Action Observation Training
MNS	Mirror neuron system
ADL	Activities of daily living
IADL	Instrumental activities of daily living
QOL	Quality of Life
HR-QOL	Health Related Quality of Life
MEPs	Motor Evoked Potentials
M1	Primary motor cortex
AD	Attention deficit
No_AD	No attention deficit

INTRODUCTION

THESIS ROADMAP



CHAPTER 1

MULTIPLE SCLEROSIS

1.1 Definition and Epidemiology

Multiple sclerosis is the most common demyelinating disease, affecting 2.3 million people worldwide according to the World Health Organisation (Multiple Sclerosis International Federation, 2013). The prevalence is region and gender dependant. North America and Europa have the highest prevalence and MS is twice more common in women compared to men. The average age of onset of MS is early (30 years) (Confavreux & Vukusic, 2008); however, the life expectancy of MS patients is only slightly lower than the healthy population (Lunde et al., 2017). Thus many patients remain affected by the disease for the majority of their adult life, which results in an enormous social and economic impact for patients, their families and carers (Multiple Sclerosis International Federation, 2013).

1.2 Risk factors

The cause of the disease is not yet established, but most likely it is the result of a complex interplay of genetics and environmental factors (Munger et al., 2006). Various risk factors have been suggested, such as smoking (Handel et al., 2011), low level of vitamin D (Munger et al., 2006), pre- vious Epstein-Barr virus infection (Handel et al., 2010a) and genetics (Willer et al., 2003; Handel et al., 2010b; Gourraud et al., 2012). Several other factors have been implicated, such as diet (Fregni, 2018).

1.3 Diagnosis

The heterogeneity in presentation can complicate the diagnosis of MS in the clinic.

There is no one single specific diagnostic test to establish MS; instead, the diagnosis is criterion-based, that is, on the McDonald criteria (McDonald et al., 2001). The basic diagnostic criterion is evidence of distribution of MS lesions in time and space. In 2010 the McDonald criteria were revised, making it possible to diagnose MS at its clinical onset, using MRI. Inflammatory-demyelinating injury is measured using a combination of the patient's clinical history, a neurologic examination, CNS imaging and exclusion of diseases with similar symptoms (Polman et al., 2011). Finally, the 2017 revised McDonald criteria further improve the dissemination in time by allowing specific measures in the spinal fluid (Thompson et al., 2018).

1.4 Pathophysiology

The pathology in MS is complex and consists of inflammation, demyelination and neurodegeneration; each pathological process plays a role in the different clinical stages of MS; however, whether they are the important driver or play a smaller role in the background varies.

MS is often regarded as an autoimmune disorder, which means that the body's immune system recognizes its own antigens as foreign and attacks its own cells. This results in inflammation within the CNS which includes the brain, optic nerves and spinal cord (Abou-Raya & Abou-Raya, 2006). The initial trigger causing inflammation in the CNS remains unknown, but the dominating theory is the CNS extrinsic or molecular mimicry theory (Malpass, 2012). Demyelination is the loss of myelin, which is the result of an immune cell mediated attack against myelin antigens (Kane & Oware, 2012). Finally, neurodegeneration is an umbrella term for the progressive loss of structure and function of neurons, and it is the strongest correlate of irreversible neurologic disability (Friese et al., 2014). Neurodegeneration is already present in the early stages of MS (Novakova et al., 2018) and the degree of neurodegeneration early in the disease may be an indicator of disease progression and outcome

(Brex et al., 2002). Lesions (also called plaques) are the regions of injury in the brain, which are caused by a combination of inflammation, demyelination, and neurodegeneration (Popescu & Lucchinetti, 2012). Lesions occurs in both white and grey matter of the CNS. The most recent classification divides MS lesions as active, mixed active/inactive, or inactive lesions based on the presence and distribution of immune cells (Kuhlmann et al., 2017).

1.5 Symptomatology

The clinical course of MS is heterogeneous and difficult to predict on the individual level. The variability in symptomatology is already presents at onset. The initial symptom or episode that brings people to the neurologist is most often a motor or sensory problem. Specifically, typical presentation of patients are unilateral optic neuritis, focal brainstem or cerebellar syndrome or partial myelopathy (Thompson et al.,2018). While the motor and sensory symptoms are more likely to prompt a consultation with a neurologist, others such as fatigue are more difficult to measure and therefore may go unrecorded. Similarly, symptoms related to urinary and sexual issues may be less likely to be discussed by people with MS in some cultures. Over time, the symptomatology of MS includes the following domains in order of most common: sensory, motor, visual, fatigue, balance, sexual, urinary, pain and cognition (Multiple Sclerosis International Federation, 2013). Even though not all symptoms present in the early stages of MS, all domains of disability worsen with disease progression (Kister et al., 2013). Progressive worsening of neurological function in the cognitive and motor domains can affect work performance and activities of daily living. This condition can lead to less independence and less social participation, negatively impacting the quality of life (de Heredia-Torres et al., 2020).

1.6 Clinical course

MS is a heterogenic disease and the course varies from person to person. The course is divided into four clinical stages of MS. There are two stages prior to clinically definite MS. There is radiological evidence to support a preclinical stage of MS, named radiologically isolated syndrome (Lebrun, Kantarci, Siva, Pelletier, & Okuda, 2018). The first clinical presentation of MS is known as clinically isolated syndrome (CIS). CIS patients present with their first episode of focal neurological symptom(s), lasting at least 24 hours, which represents an area of inflammation or demyelination in the optic nerve, brain (Marcus & Waubant, 2013) or spinal cord (Arrambide et al., 2018). The first relapse following CIS denoting the transition from CIS to relapsing-remitting MS (RRMS). Diagnosis of RRMS can also be made substituting dissemination in time and space using imaging features of lesion distribution and the development of new lesions (Polman et al., 2011). RRMS is the most common type of MS with 85% of patients diagnosed with this phenotype. Clinical relapses are followed by periods of remission (periods of partial or complete recovery) and no progression between relapses. Progression of disability still occurs by incomplete recovery after relapse, this is a sign of poorer prognosis and earlier development of secondary progressive MS (SPMS) (Novotna et al., 2015). In historical epidemiology studies, 80% of all RRMS patients eventually lose the stable periods between relapses and show irreversible progression, which marks the transition to SPMS. One third of patients with SPMS experience relapses and the disease course can plateau for period of stability and then further progression. In addition, about ten to fifteen percent of patients present with primary-progressive MS (PPMS). PPMS is characterized by a steady progression of disability from the onset of symptoms without prior periods of relapses or remission (Thompson et al., 2018). Fluctuations of progression rate, periods of stable disease and relapse might still occur.

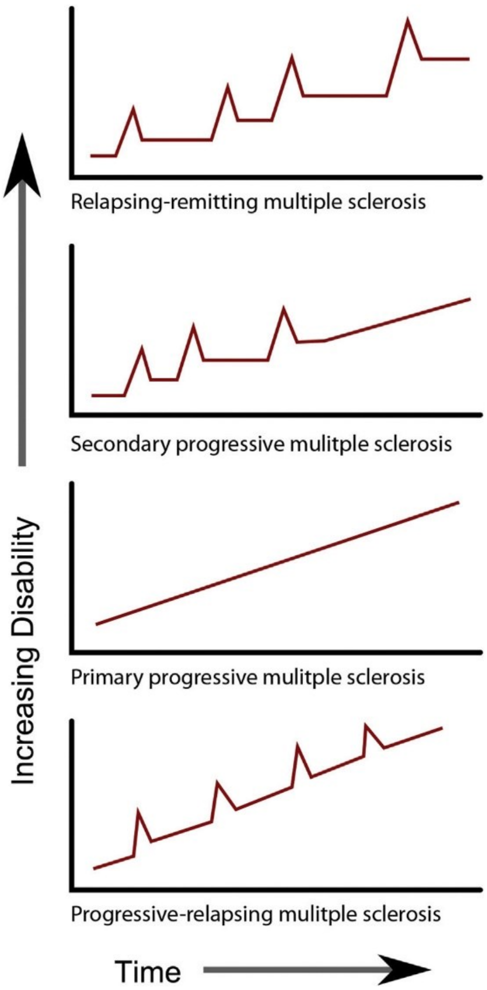


Figure 3. The four classic disease course phenotypes in multiple sclerosis (Krieger & Sumowski, 2018)

1.7 Prognosis

The phenotype is important in prognosis due to difference in severity and recovery after an acute relapse. Relapses involving the pyramidal and bowel/bladder function result in a bigger change in disability and are therefore regarded as more severe (Stewart et al., 2017). Furthermore, complete recovery of function is more likely after sensory, visual and brainstem episode, compared to pyramidal, bowel/bladder, cognitive and cerebellar episodes (Kalincik et al., 2014). Kalincik et al. (2014) showed that females experience more repeated relapses, however, they often involve the sensory and visual functions. Contrarily, men are thought to have fewer relapses, but they more often affect pyramidal, brainstem or cerebellar functions. This indicates that women, who are more likely to experience more frequent but less severe relapses with better recovery, will also show better long-term disease outcomes than men.

1.8 Pharmacological Therapy

Multiple sclerosis therapy is based on three aspects: acute attack therapy to limit the damage caused by inflammation; basic therapy to modulate the functioning of the immune system and symptomatic therapy to treat symptoms secondary to the disease.

The therapy of the acute attack, or new neurological deficit or its worsening lasting more than 24 hours in the absence of infections, is based on the use of corticosteroids. The goals of this therapy are to reduce the duration of this relapse, reduce the risk of permanent post-attack neurological deficit and reduce the risk of a new attack. In cases where first-line corticosteroid therapy is accompanied by worsening of symptoms, plasmapheresis is recommended.

The basic therapy is based on drugs that go under the term of Disease Modyfing Therapy (DMT). Their role is to modify the natural course of the disease by reducing the number and frequency of relapses, and by improving the outcome in terms of disability. Two groups of drugs can be distinguished: immunomodulating drugs and immunosuppressive drugs. Generally, basic therapy is started with immunomodulating drugs (eg interferon-β and Glatiramer acetate), defined as first-line. Their main purpose is to limit the disturbance to the immune system and to suppress inflammatory attacks that damage myelin in the CNS. These drugs have been shown to reduce the frequency of relapses by 30% and the progression of disability in the short term. Immunosuppressants are second-line drugs (Natalizumab, Fingolimod, Azatiopirina), used in case of relapses during immunomodulatory therapy. These are drugs capable of inhibiting cell division by blocking key components of DNA duplication or repair mechanisms, resulting in an inability of cells to duplicate at a normal rate.

Finally, symptomatic therapy includes all treatments for secondary manifestations of MS. In managing symptoms, it is important to balance the benefits of a treatment with the risks of adverse effects related to drugs. For spasticity, centrally acting muscle relaxants (e.g. Baclofen, Tizanidine, Benzodiazepines) are generally used**.** To improve motor performance, especially walking, there is Fampridine. Among the molecules useful for the control of fatigue are Amantadine and Fluoxetine. As for neuropathic pain, the most commonly used drugs are Carbamazepine and Gabapentin. The pharmacological approach to cognitive disorders was mainly limited to the use of cholinesterase inhibitors. It should be considered that the treatment to control the course of the disease could stop or reduce the progressive cognitive deterioration **(**Zajicek, 2001; Canal et al., 2011; Wei et al., 2021).

1.9 Clinical evaluation

Worldwide, neurological impairment and MS severity are common evaluated by neurologists using the Expanded Disability Status Scale (EDSS); it is a disease-specific instrument that has become the gold-standard for characterizing disability levels and determining disability progression in patients with MS. The scale was developed in 1983 and ranges from 0 to 10 (0 equals a normal neurological examination and 10 represents death due to MS). Scores of 0–3.5 are based on the examination of eight different functional systems: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral and other. Scores from 4 and above are based on the person's walking ability. The assessment of walking is based on maximum distance walked up to 500 m and the use of an assistive device. However, wide variability was observed in maximum distance walked within each EDSS level, with patients with high level of disability that often walking the same maximum distance as those with low level of disability (Bethoux et al., 2011). MS can be graded as mild at EDSS 0 to 3.5, moderate at EDSS 4.0 to 5.5 and severe at 6.0 to 9.5 (Kurtzke, 1983).

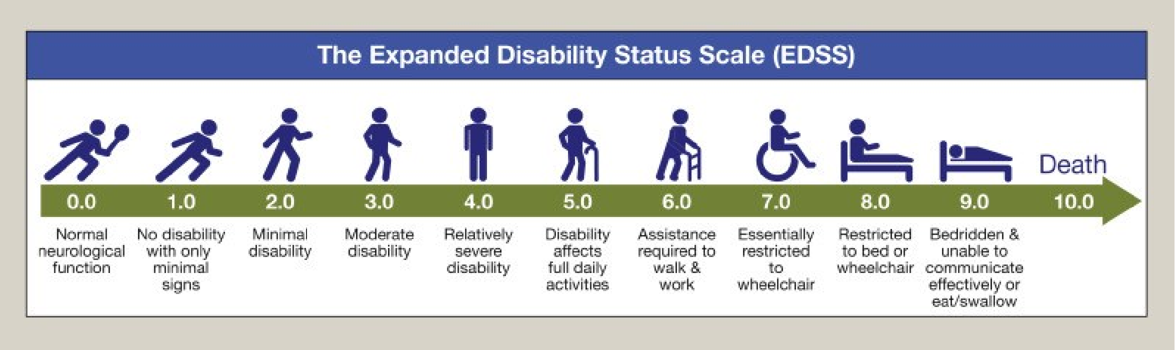


Figure 4. The Extended Disability Status Scale (EDSS) (Kurtzke, 1983)

Other measures exist to assess the dysfunction in people with MS. It can be evaluated using standardized clinician-assessed rating scales, performance tests, self-report questionnaires, observational analysis or 3D analysis. In the following session, the most common clinical measures for the evaluation of gait, balance and quality of life alterations in MS patients are briefly described.

- Timed walking tests. Albeit these tests are not MS-specific, they have demonstrated good reliability and reproducibility in these patients to provide a quantitative measure of walking performance (Nilsagard et al., 2007). Among the timed tests, the timed 10-meter walk and the 6-minute walk test are the most widely employed, these are considered a reliable measure of walking endurance. Also exists a shorter version of the test, the 2-minute walk test, with a greater feasibility and reduced patient burden (Van den Berg et al., 2006). Also, the timed 25-foot walk test was not developed as a MS instrument, however it correlates with the EDSS across disability severity and MS subtypes (Kalkers et al., 2000). This tests correlate strongly with overall measures of disability, including the EDSS and with a patient-reported measure of walking, i.e. the 12-item Multiple Sclerosis walking scale (MSWS-12) (Goldman et al., 2007).
- Figure of eight walk test (F8WT). It measures the everyday walking ability of adults with mobility disability. The F8WT tests a participant's gait in both straight and curved paths. The F8WT uses a path where the participant is asked to walk a figure of eight shape around two cones. Scores are recorded in three areas: speed (time for completion), amplitude (number of steps taken), and accuracy or "smoothness" (Song & Kim, 2018).
- The Dynamic Gait Index (DGI). Is a clinical scale composing of 8-item; the total score depending on the rater's observation of the degree of limitation during a patient's performance of specific tasks (Shumway-Cook & Woollacott, 1995). Though this tool was primarily designed to assess the likelihood of falling in older adults, it provides an overall assessment of ambulation also for MS patients, with the presence of the items of walking, stair climbing and balance.
- Timed Up & Go Test (TUG). It is a tool for measuring balance and functional mobility. Specifically, this test timing the patient when get up from a chair, walk a distance of 10 feet, make a 180-degree turn around a cone, and then sit back down. Those measures are important for activities of daily living and the maintenance of independence (Sebastião et al., 2016).
- Functional Reach Test (FRT). This test aims to evaluate the balance at the stability limits. It testing the ability to maintain balance in an upright position with the center of gravity moved forward, arms forward and shoulders in 90 ° flexion is tested. It measures the maximum distance that the patient can reach without falling three times, the average of the last two measurements is considered. Greater distances indicate better postural control (Duncan et al., 1990).
- Four Square Step Test (FSST). This tool evaluates the dynamic balance in people with MS. The patient is asked to move one step at a time in each of the 4 quadrants identified by a cross-shaped indicator placed on the floor; this sequence is performed both clockwise and anticlockwise. Two repetitions are performed, and the best time is considered. Shorter times indicate a better ability to control dynamic equilibrium (Wagner et al., 2013).
- Berg Balance Scale (BBS). Evaluate the ability to maintain static and dynamic balance. It includes 14 motor tasks of common application in daily life, such as controlling the upright posture (even in conditions at the limit of stability, for example on one leg), picking up an object from the floor, turning around, etc. Each item is rated on a numerical scale from 0 (impaired function or need of assistance) to 4 (full autonomy) (Berg et al., 1992).
- Posturographic evaluation. Posturography assess a standing patient's capability to keep balance; is consider an objective technique for measuring postural strategies in static and dynamic conditions. It is also used to differentiate the contributions of the visual, vestibular, and proprioceptive systems to a patient's balance. The patient is placed on a platform while the sensors within the platform footplate measure the force exerted from the feet when the patient's center of gravity is displaced (Vanicek et al., 2013).
- Multiple Sclerosis Walking Scale - 12 (MSWS-12). It is a patient-based tool designed specific for MS, used to capture the complex impact of disease on walking abilities (Hobart et al., 2003). It consists of 12 questions with Likert-type responses and has a recall period of two weeks. Its most relevant attribute is its responsiveness to change (Hobart et al., 2003). Many studies demonstrating high reliability and validity, and good generalizability of this tool (Motl et al., 2007). Furthermore, it is correlated with the EDSS and with several objective measures of mobility (i.e., number of step count performed in a given time period, gait speed) (Hobart et al., 2003; Motl et al., 2008).
- Multiple Sclerosis Impact Scale - 29 (MSIS-29). It is a self-administered questionnaire that assesses the patient's perceived impact of MS in the two last weeks. Specifically, it evaluates two domains: physical (items 1-20) and psychological (items 21-29). The first comprehend items that regards limitation in carrying out strenuous tasks, balance problems, feeling of stiffness,

awkwardness, heaviness in the limbs, tremors or spasms, limitations in everyday activities, etc. Psychological domain comprends the evalutation of functions as sleep disturbances, mental fatigue, worry or anxiety, distrust, depression, irritability, urinary urgency, etc. Higher values correspond to a greater impact on function (for each single item 1-not at all, 5- extremely) (Hobart et al., 2001).

- Modified Fatigue Impact Scale (MFIS). Is a self-report questionnaire that evaluate the impact of fatigue on physical, cognitive and psychosocial functioning in the last 4 weeks. Examples of items that are evaluated are the level of vigilance, the level of attention, physical embarrassment, motivation, decision-making ability, concentration, clarity of thought, etc. Higher scores correspond to a higher impact of fatigue (for each single item 0-almost never, 4-always) (Fisk et al., 1994).

1.10 Balance, gait and falls in Multiple Sclerosis

Multiple Sclerosis involves a wide range of neurological dysfunctions that result in limited mobility, i.e. in walking and balance in the advanced stages of the disease (Compston et al., 2008), but sometimes also in the early stages of newly diagnosed disease in the absence of other clinical disabilities (Martin et al., 2006; Casadio et al., 2008). Maintaining an upright position and balance requires the interaction of multiple sensorimotor systems (visual, vestibular, proprioceptive) to generate coordinated movements that keep the center of mass within the Limits of Stability (Shumway-Cook et al., 2005). Alterations in balance and walking are common findings in people with MS (Comber et al., 2017; Cameron & Nilsagard, 2018). Many people fall frequently or fear falling and the risk of trauma resulting from the fall is significant. The risk of falling is also increased in association with walking with the use of supports (crutch or medical walker) (Nilsagård et al., 2009; Cameron & Lord, 2010).

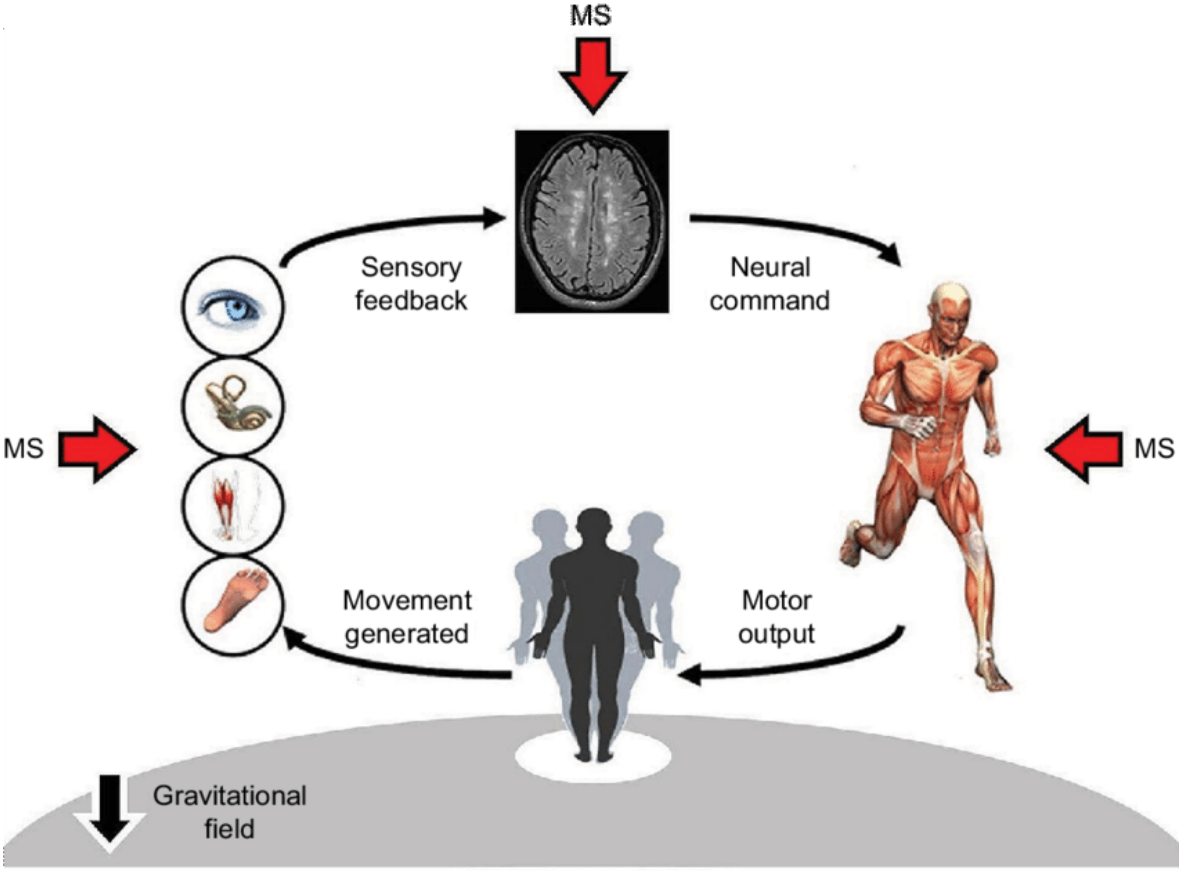


Figure 5. Schematic of postural control and its alterations in Multiple Sclerosis (Prosperini & Castelli, 2018)

1.10.1 Balance

Balance is a complex task that need several varied ability, motor (e.g. flexibility, strength), sensory (e.g. proprioception, vestibular system) and cognitive (e.g. attention, concentration) (Shumway-Cook & Woollacott; 2007). Interactions among these functions are integrated to keep balance. There is not worldwide accepted definition of term "balance", it can be seen as a blanket term that encompasses stability, balance control, postural control, and alignment (Pollock et al., 2000; Shumway-Cook & Woollacott, 2007). In the International Classification of Functioning, Disability and Health (Svestkova, 2008) not exist a specific code for balance, however, the complexity of balance can be understood across the components of the framework. Balance can be affected by broken body functions or structures, it also depended on which activity is to be performed, which in turn can influence participation; contribute also personal factors (e.g. balance confidence), and environmental factors. The cerebral cortex plan and program the body movements. That is, sends its commands (motor output) to the skeletal muscles of the body where the actual movement is performed. Information about the movement planning is also sent to the cerebellum, which is the motor control center of the body: it coordinates and regulates posture, movement, and balance. Moreover, the cerebellum gain sensory input from the muscle spindles and the Golgi tendon organs, which give feedback of the muscle length, speed and tension; from sensory touch via the cutaneous receptors; from vision; and from proprioception via the joint receptors. Following receipt the sensory input, the cerebellum value the performed movements, and, if necessary, regulate the position of the body components (Shumway-Cook & Woollacott; 2007). Depending on the task to be performed, there are various facets of balance. Static balance is characterized by small amounts of spontaneous postural sway and consist of the capability to preserve an upright position without changing the base of support. Dynamic balance, instead, is the ability to maintain balance during movement. Proactive balance is the capacity to arrange the body for the movement first the movement is performed (i.e. feed forward). Since the voluntary movements in themselves can be destabilizing, the stabilizing muscles are activated to minimize instability during a movement. Reactive balance, instead, occurs when the body has to react to something unforeseen. This enact the ability to regain balance after an unexpected disturbance and to move defensively to preserve balance and avoid falls (Shumway-Cook & Woollacott; 2007).

Balance impairment is a common and often early symptom in MS. Over 80% of the patient report their balance to be compromise, 15% report a fluctuation of balance, 67% report the impairment to be constant (Isaksson et al., 2005; Martin et al., 2006). Cameron and Lord (2010) remark three different aspects of balance typically present in MS. First, a decreased ability to maintain position, indeed, in these patients there is an increased postural sway and more difficulties in maintaining position when the base of support is reduced or limited. Patients with a higher EDSS score, i.e., a more severe impairment and having a progressive MS form, have an increased postural sway compared to those with a mild impairment and with relapsing-remitting MS form. Patients with MS do not use the equal strategies to keep balance as age-matched healthy controls without walking limitations do, hence the increased sway (Huisinga et al., 2018). Secondly, Cameron and Lord (2010) delineate MS patient possess limited and slow movement toward their limits of stability. In fact, when trying to reach or step, they move less far and less quickly. These patients also have a reduced functional reach distance. Third, MS patient have delayed responses to postural displacements or perturbations, a poorer trunk control and delayed postural responses when the surface is moving (Cameron and Lord, 2010). It has also been description an impaired trunk stability while sitting on an unstable surface in MS as to healthy controls (Lanzetta et al., 2004). Trunk control comprehends coordination of active (i.e. muscles), passive (i.e. lumbar spine) and control (i.e. neurological system) aspects. Muscles that are believed to set up trunk control are the transvers abdominis, the multifidus and the pelvic floor muscles (Hoffman & Gabel, 2013). All of these muscles are valuable for the trunk control depending of the situation and position of the body; stability and movement of the body are critically dependent on the coordination of all the muscles which together form the core (Akuthota & Nadler, 2004). A systematic review reported that postural control in patient with MS is impaired, indipendently of the complexity of the task performed (Comber et al., 2018). The three aspects of impairments present in people with MS enclose static and dynamic, as proactive and reactive, balance (Cameron & Lord, 2010). A fourth aspect to be commonly impaired in MS is dual tasking: having to split one’s attention while performing a balance-requiring task can influence the balance negatively (Nilsagard et al., 2009; Wajda et al., 2013; Etemadi, 2017). Balance impairment can

conduct to everyday life restrictions and diminish in social participation (Nilsagard et al., 2012; Cattaneo et al., 2017).
Generally, balance requires motor, sensory and cognitive skills to be attained. All different aspects of balance, impaired body function or structure, are to be measure to provide a description of each individual's strengths and limitations and enables the practitioner to evaluate the better intervention; as well as measure the outcome of this in daily life. The ICF model has been recommended to structure evaluation of imbalance in MS (Cameron & Nilsagard, 2013).

1.10.2 Falls

The result of not being able to maintain one's balance is to experience a fall. Falls, as balance, are of complex nature (Peterson et al., 2013). Fall is defined as "an unexpected event in which participants come to rest on the ground, floor, or a lower level" (Lamb et al., 2005). Fall risk in MS is commonly high. A peak for fall risk has been suggested at EDSS scores in which walking transitions are likely, i.e. score 4.0 and 6.0 (Nilsagard et al., 2015). A meta-analysis report a fall frequency of 56% during a 3 months period in patient with an EDSS score between 1.5 and 7.0. Of those signaling fall, 37% were frequent fallers. Most of the falls have been reported to occur during daytime (75%) and indoors (65%), during transfers (80%) and during walking (60%) (Matsuda et al., 2011). Men fall more frequently than women (Nilsagard et al., 2009; Gunn et al., 2014). Differences between fall and non-fallers have been reported in the dynamic balance: fallers walk slower and with more caution, has a greater variation in step length, and the foot is kept closer to the ground during the swing phase (Peebles et al., 2017). A meta-analysis evidence an increased risk of fall associated with balance impairment, cognitive deficits, progressive MS and use of mobility aids (walking aids or wheelchair) (Gunn et al., 2013). Risk factors of falls can be classified as either intrinsic or extrinsic. Examples of extrinsic factors are the environmental factors, such as slippery or uneven surfaces, or malfunction or non-use of walking aids. Among intrinsic fall risk factors in MS there are lower extremity malfunction, limited walking abilities, and reduced muscular endurance, not paying attention, divided attention deficit, fatigue, and heat sensitivity etc. (Nilsagard et al., 2009; Peterson et al., 2013). Another intrinsic fall risk factor is the fear of falling, reported in over 60% of MS patients. Are more likely to report fear of falling the women, person who have reported having fallen during the last 6 months and who use a walking aid. Fear of falling can lead to limit or avoidance of activities that the patient would still capable of managing; in fact more than 80% expressing fear of falling experience curtailment of activity. Such activity reduction can in turn driving to greater fall risk, producing a negative spiral (Peterson et al., 2007).

1.10.3 Gait

Although a wide range of factors can concur to gait dysfunction in MS, the principally contribute to this abnormality are due sensory changes and resulting balance deficit, lower extremity weakness or spasticity, and cerebellar ataxia. Diverse studies demonstrate that MS patients, already in early stage of the disease, present gait abnormalities such as decreased step length and cadence, reduced joint motion, and more variability of most gait parameters compared to healthy controls (Martin et al., 2006; LaRocca, 2011). These abnormalities involve reduce walking endurance, an increase metabolic cost of walking, and reduce community mobility (LaRocca et al., 2011). Moreover, these patients while performing a cognitive task, reducing their walking speed and increase the gait variability more than healthy controls. This denoting the need to dedicate greater cognitive reserve to ensure dynamic stability during walking in MS patients (Leone et al., 2015).

1.11 Neurocognitive and psychological impact in Multiple Sclerosis

Besides the aforementioned deficits, MS leads to mood and cognitive disturbances.

1.11.1 Psychological disturbances

Persons with MS appear to have a higher prevalence of a number of psychiatric symptoms and disorders: major depressive disorder, any anxiety disorders, generalized anxiety disorder, bipolar disorder, alcohol abuse, substance misuse (Chwastiak & Ehde, 2007). The most common of these remains anxiety and depression. The prevalence of depression during the lifetime in MS patients varies between 30% and 40% (Boeschoten et al., 2017). Depression tends to not be related to the severity of the disease instead to the unpredictable course and prognosis, indeed depression is less frequent in individuals with a progressive form than in the relapsing-remitting form (Zabad et al., 2005). Other psychosocial factors associated with depression are lower education, shorter duration of illness, perception of limited social support (Hanna & Strober, 2020). Among the biological factors, a correlation has been shown between the topography of demyelinating lesions and depression (Feinstein et al., 2004); regarding the immunological markers, an increased risk of depression is associated with an elevated CD4 + T helper lymphocyte count (Foley et al., 1988). Anxiety disorders occur in 36% of individuals with MS (Korostil & Feinstein, 2007). The aetiology includes biological and psychosocial factors. Among the first are alterations in the neuronal circuits involving the amygdala, the basal ganglia, the cerebral cortex and a dysregulation of different neurotransmission systems (Bystritsky et al., 2013). Regarding psychosocial factors, there are: female sex, shorter duration of the disease, lower disability levels, younger age of onset and previous diagnosis of depression. A higher rate of substance abuse, greater social stress, and limited social support have also been reported (Hanna & Strober, 2020). Anxiety and depression lead to worsening of symptoms, thus the functional status, to increased drug use, lower employment rate, to decreased adherence to treatment thus reduced efficacy of therapeutic interventions, increased suicidal ideation and finally, to lower quality of life (Hanna & Strober , 2020). The diagnosis of anxiety-depression comorbidity is very common in people with chronic diseases (Km et al., 2007). The presence of such comorbidity in MS patients has greater consequences than the presence of depression or anxiety alone, particularly with regard to quality of life, the extent of symptoms, suicidal ideation and social functioning (Feinstein et al. ., 1999). These mood disorders continues to be under-detected and under-treated by MS providers. Treatment with pharmacotherapy is particularly challenging in this patient population, given the somatic symptom overlap between MS and mood disorders, and the increased burden of side effects. However, psychological intervention should be indicated (e.g. mindfulness-based intervention, cognitive-behaviour psychotherapy, relaxation training). MS is also associated with alexithymia, a characteristic personality construct characterized by the difficulty of identifying and describing one's feelings. The imaginative processes of the individual are limited and an external-oriented cognitive style prevails, i.e. the subject neglects the internal dimension to the advantage of external reality (e.g., misinterpreting an emotional phenomenon as a symptom of physical illness) (Bodini et al., 2008).

1.11.2 Cognitive impairment

Cognitive impairment in MS is frequent, affecting up to 65% of patients (Rao et al., 1991; Amato et al., 2006). It is visible at all subtypes and stages of the disease (Potagas et al., 2008), including in clinically isolated syndrome (CIS) (Khalil et al., 2011). In relapsing-remitting MS form, the cognitive dysfunction's prevalence is estimated to 22-40% (Potagas et al., 2008; Patti et al., 2009), while patients with primary-progressive and secondary-progressive forms incline to have an higher frequency of cognitive impairment (Huijbregts et al., 2006). Cognitive impairment in MS ordinarily persists and aggravate over time (Bagert et al., 2002; Amato et al., 2006). The study of MS-associated cognitive impairment is fundamental considering its detrimental effects on numerous activities of daily life as physical independence, symptom management, medication adherence, rehabilitation potential, coping ability, employment, and driving safety (Langdon, 2011). Thus, it was confirmed the necessity of a formal neurocognitive assessment, especially due to the fact that patient's perception about their cognitive performance is unreliable and not predictive of objective cognitive functioning (Middleton et al., 2006; Julian et al., 2007).

Cognition includes many aspects of complex mental functions, is not a uniform entity. Several domains of cognitive functioning can be affected in MS, there are deficit in attention, executive functions and memory. Also verbal fluency, but not core language abilities, is often reduced in MS. However, impaired information processing speed and learning and memory are often defined the major deficits (Chiaravalloti & DeLuca, 2008). It was strongly recognize the importance of cognitive impairment in MS and there is an overall consensus about the general deficits profile but not about the clinical risk factors. Seems that cognitive impairment may exist independently of physical disability (Cobble, 1992). Previous studies showed a weak or absent correlation between duration of MS and cognitive impairment (Rao et al., 1991; Lynch et al., 2005; Patti et al., 2009; Chiaravalloti

& DeLuca, 2008). Other studies, instead, have found a modest/moderate association between level of physical disability and cognitive performance (Beatty et al., 1990; Lynch et al., 2005; Patti et al., 2009), but this relation is probable to be less noticeable or lacking when the level of physical disability is lower (Prakash, 2008). Moreover, also mood disturbance could be possible clinical risk factor in cognitive impairment. An association has been demonstrated, especially between depression and the information processing speed and executive functions (Arnett et al., 2008; Siegert & Abernethy, 2005; Feinstein et al., 2006). In MS patients, cognitive performance was correlated with the non-somatic components of depression (Beatty, 1998; Arnett et al., 1999). Despite this, the relationship between depression and cognitive impairment has not clarify (Chiaravalloti & DeLuca, 2008).

Also relative to fatigue in MS, there are incongruence in literature. Andreasen et al. (2010) reported an association between fatigue and decreased information processing speed; instead, other studies did not find subjective fatigue to be related with cognitive impairment (Bol et al., 2009; Morrow et al., 2009). Also use in MS patients of CNS-active psychotropic drugs against depression, pain, and insomnia may have effects, negative or positive, on cognitive performance.

1.12 Cognitive-Motor interference

The ability of the CNS to process information is limited and this affects the ability to plan and carry out multiple tasks at the same time (Marois & Ivanoff, 2005), so the CNS must adapt to the demands of the environment, shifting attention to the most relevant information every moment for the task in progress (McIsaac et al., 2018).

This limitation, although present also in healthy subjects, becomes more evident in subjects with neurodegenerative diseases. MS affects both cognitive and motor functioning, patients are in fact particularly susceptible to cognitive-motor interference in the dual task (Beatty et al., 1995). The dual task shifts the subject's attention to an external source of attention while the subject performs a main task. The need for simultaneous activation of multiple cortical areas to achieve optimal performance in the dual task suggests that neuronal cortical degeneration in MS patients is related to specific interference effects in the dual task (Rao et al., 1991).

1.12.1 Reinvestment Theory and constrained action hypothesis

Postural stability is an integral component of motor control and body coordination processes, and is required during static and dynamic balance activities (Wikstrom et al., 2005). This component is the result of proprioceptive afferents and complex sensorimotor integrations (Goble et al., 2008; Vaugoyeau et al., 2008; Ghai et al., 2017); it is mediated both by a higher level of control, which engages the cortical circuits and basal nuclei, and by an automated lower control that engages the brainstem (Jacobs & Horak, 2007; Honeycutt et al., 2009; Boisgontier et al., 2013).

Some studies suggest that any alteration in conscious attention towards postural control can interfere with coordination and stability, because of the movement-specific reinvestment of attention. The theory of reinvestment assumes that the need to direct attention internally to control movement can lead to an alteration of performance. This phenomenon does not occur in the healthy subject, where movement control is an automatic process, but increases with aging and in neurological diseases (Masters, 1992; Wulf et al., 2001; Masters & Maxwell,2008; Schaefer et al., 2015). Some studies confirm these hypotheses and associate the shift of attention towards an internal focus with aging and the loss of gray or white matter in the CNS that involves differential-reorganized cortical activation (Seidler et al., 2010). The latter can interfere with the priority assigned to tasks, increasing the demand for conscious attention during the performance of a motor or cognitive task (Talelli et al., 2008). It has been hypothesized that the use of an internal focus of attention (on one's own movements) interferes with the automatic control processes, which would normally take care of regulating the movement, while an external focus of attention (on the effect of the movement) would allow a more natural / automated performance of motor task (Wulf et al., 2001).

This is the so-called "constrained action hypothesis" and argues that the intentional shifting of attention to an external focus can affect the motor systems in automatic functioning, resulting in a more effective performance. Several studies have shown the possibility of practical applications for the enhancement of automation, evaluating complex motor skills, postural stability and walking (Beilock & Carr 2001; Resch et al., 2011; Ghai et al., 2017; Schaefer et al., 2015). An increase in cognitive commitment and in cognitive-motor interference was observed as the complexity of the task increased. This increase in central interference negatively affects both motor and cognitive performance (Montero-Odasso et al., 2009; Boes et al., 2012; Lanzarin et al., 2015). Several studies have investigated the benefit of motor training and dual task for the enhancement of cognitive and motor performance (Silsupadol et al., 2009; Hiyamizu et al., 2012; Gomez-Pinilla & Hillman, 2013; Zanotto et al., 2014; Gobbo et al., 2014; Choi et al., 2015). Furthermore, positive effects have been reported in subjects at risk of falling (Bherer et al., 2005).

It is believed that the change in the regulation of motor activity allows the automation of motor tasks thanks to a structural displacement (Heuer, 1984). With the latter, the control of the operation, motor planning and executive functions would become the responsibility of a lower-grade processing center, reducing the cortical effort for motor control (Blischke et al., 2010). The studies conducted through neuroimaging reveal the activation of specific brain areas during the performance of dual task, such as the anterior cingulate cortex, the prefrontal cortex and the inferior frontal gyrus (Schubert & Szameitat, 2003; Collette et al., 2005).

1.12.2 Theoretical models of dual-task interference

The presence of cognitive-motor interference occurs when in one or both tasks a worsening is observed during the execution of the task performed simultaneously with respect to the results of the tests performed individually (Leone et al., 2015).

Cognitive-motor interference can be expressed in terms of dual task cost (Dual Task Cost - DTC) (Baddeley et al., 1997), calculated as:

$$DTC = \frac{(single\ task - dual\ task)}{single\ task}\ x\ 100$$

Although the precise mechanisms underlying the cognitive-motor interference are not fully clarified, some theories have been advanced.

The three theoretical frameworks exploited to describe interference between tasks are: the serial bottleneck model, the capacity sharing model and the crosstalk model. The first one concerns the idea that certain critical mental operations are perform sequentially. When this restriction applies, the interference emerges since certain tasks demand concurrent access to a processor that can only finalize one task at a time (Pashler, 1994). Through the time that of one task is occupying the bottleneck process, there is a postponement of the elaboration of one task on the other one (Pashler and Johnston, 1989). Contrary, the capacity sharing model considers that individual has a finite attentional capability (Wickens, 1980) and that both motor and cognitive tasks demand a certain quantity of attentional resources to be done well. It is presumed that multiple tasks can proceed in parallel, why less resources are available to each task under these conditions, and thus the tasks progress at a reduced rate (Tombu & Jolicoeur, 2003). If the combined attentional requirements of the tasks are highter than the capacity reserve, there is a declension in one or both tasks. Finally, the cross-talk model supposes that interference might be depending not on what sort of operation is performed but on the content of the information actually being elaborated (e.g., what sensory inputs are present). All those models give great different depiction of our mental machine: the capacity model conclude that task can be processing simultaneously, while bottleneck model assume that some processes can be handled strictly serially and the cross-talk model supposes that carrying out concurrently similar tasks reduce dual-task interference, since the acquisition of the same pathway growing the processing efficiency and are recruited less attentional resources (Pashler, 1994).

1.12.3 Balance and cognitive functioning

Cognitive functions play a critical role in the performance of motor tasks, including the maintenance of static and dynamic balance. Although a balance disorder is traditionally assumed to result from lesions of neuromuscular and musculoskeletal components, it is possible that it is related to a cognitive deficit (Fjeldstad et al., 2011). In the MS patient population, the role of higher cognitive processes in maintaining balance has been poorly investigated (Negahban et al., 2011). The most common method for assessing the inference of cognitive processes (particularly attentional and executive mechanisms) on balance is "dualtask performance," which consists of performing two tasks simultaneously (Woollacott & Shumway-Cook,2002; Fraizer & Mitra, 2008). Therefore, reference is made to models that theorize a central resource of attention, such as Kahneman's model which states that human has a limited capacity to perform mental tasks. For this reason, as the demands increase, there is a corresponding increase in the number of resources mobilized, until the first exceed the second: at this point the performance is no longer adequate to the demand and there is an interference between tasks (Kahneman, 1973). Because more attention directed toward maintaining balance is needed in MS patients, simultaneous performance of a competing cognitive task will lead to impairment in one or both performances (Fjeldstad et al., 2011). The greater the impairment, the greater the deterioration in performance (Monticone et al., 2014). Significant differences were observed with respect to the healthy population in the speed of postural oscillations. The velocity decreases when, with eyes closed and standing on a non-rigid surface, a competing cognitive task is asked. The fact that the speed of the oscillations decreases could be related to a reduced flexibility and ability to react to mechanical perturbations by the system responsible for postural control (Negahban et al., 2011). Considering that "dual-task performance" is frequently compromised in the population affected by MS (Chiaravellotti & De Luca, 2008), and given that in most activities of daily life, whether simple (primary ADLs) or complex (IADLs), it is necessary to perform more than one task at a same time, it is reasonable to assume that a rehabilitation program cannot consider separately the cognitive and motor aspects.

1.13 Rehabilitation interventions in Multiple Sclerosis

Great improvements have been done in terms of pharmacologic and non-pharmacologic interventions to improve dysfunction in MS population. Nevertheless, interventions to ameliorate MS related symptoms remains a meaningful clinical goal. The best action could be consist of a multidisciplinary rehabilitation approach that provide a coordinate programme delivered by a specialised team. Among these therapies, there are: drug therapy, physiotherapy, occupational therapy, speech and language therapy, social work, educational, nutrition, and psychological and cognition intervention (Amatya et al., 2019). Several studies have exposed positive results of physical intervention, as active or passive exercises, in ameliorate diverse aspect of mobility and balance in MS (Cattaneo et al., 2007; Sandroff et al., 2014). Concerning the type of exercise, aerobics, flexibility, strengthening exercise and yoga, are result beneficial on both disease symptoms and general fitness in MS patients with mild and moderate disability, as well as on quality of life (Snook & Motl, 2009). Furthermore, multimodal interventions are designed to engage simultaneously physical, sensory, and cognitive components; some technologies (e.g., brain stimulation) would be able to work as a priming and/or boosting (Bisht et al., 2017; Jonsdottir et al., 2018).

There are several methodologies of rehabilitation treatment in MS that can be individualized for each patient; some of them are described below.

- **Robot-assisted rehabilitation.** The intensity, specificity, and progression of specific motor exercises represent ideal stimuli to the neuronal reorganization process and are exploited by robotic aids for both gait recovery (e.g., exoskeletons, robotic gait assistance, treadmill training with body weight support) and upper limb (e.g., Armeo Power). The use of robotic aids on MS has shown an increase in walking performance endurance in patients with advanced disability (Beer et al., 2008) and walking speed compared with a conventional intervention (Straudi et al., 2013). A study by Carpinella et al. (2009) reported positive effects on fluidity and spatiotemporal extension of the upper extremity in patients with MS.
- **Virtual Reality**. It permits to patients to immerse themselves in a simulated experience of a real environment. The perception of being inside an everyday scenario, receiving feedback during the interaction, allows the patient to perform everyday actions going to promote the re-learning of motor patterns and reinforce their maintenance. The effectiveness demonstrated in MS populatation is not univocal; the most encouraging effects are those that have concerned the recovery of balance and walking speed (Brichetto et al., 2013; Peruzzi et al., 2016).
- **Stabilometric platform.** Patients are challenged to shift and control their centre of gravity across an interactive balance game and other rehabilitative training strategies. It is characterized by an interactive teaching model. It results ideal for vestibular training, emphasizes specific movement patterns, encourages proprioception and motor control.

- **Task Oriented Circuit Training.** It is designed for the purpose of facilitating motor learning, improving function by training gait, balance, and mobility (Kleim & Jones, 2008). The exercises are developed along different work stations, the difficulty is progressively higher and adapted to the individual. Functional exercises reflect activities that are normally performed during daily life, such as walking while maintaining a certain trajectory, overcoming a small obstacle, climbing steps, and maintaining balance during specific movements. The benefits in the MS population have been confirmed in several studies: an improvement in walking and balance has been observed at the end of two intensive weeks of treatment in patients with EDSS score 4-5.5; including an improvement in quality of life and a decrease in the perception of fatigue (Chisari et al., 2014). A favorable element is the possibility of doing the circuit also in small groups (usually 3 people). Comparison and friendly competition among patients with the same pathology positively affect motivation and increase awareness of one's own health condition (English C, Hillier, 2010).
- **Non-invasive brain stimulation techniques**

  The aim of any type of rehabilitation is to improve clinical symptomatology by modulating neuronal activity, provoking long-lasting effects over the time (Leocani et al., 2019). To reaching this aims, also non-invasive brain stimulation (NIBS) techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial electrical stimulation (TES), have been proposed as valid tools to treat neurological conditions, primarily for the potential synergy with neurorehabilitation and as additional treatment for the common neurological symptoms, for examples fatigue and neurocognitive deficits (Kobayashi & Pascual-Leone, 2003; Woods et al., 2016). Both rTMS and TES demand the employment of electric fields capable of modulating the dynamics of cortical networks. The more common form of TES techniques is transcranial direct current stimulation (tDCS): it is a non-invasive, ease of use and portable option, low cost and for a wide gamma of clinical application (Brunoni et al., 2012). tDCS requires the application of a constant low amplitude electric current (ranged from 1.0 mA to 2.5 mA) across scalp electrodes (Woods et al., 2016).

  During standard tDCS, with a pair of pad electrodes, direction of the current flow differentially modifies the resting membrane potential in both cortical and sub-cortical brain areas (Nitsche & Paulus, 2000). Anodal tDCS leading to depolarization of neuron, growing the probability of action potentials occurring, whereas cathodal stimulation leading to neuron’s hyperpolarization, decreasing the probability of action potential occurring. tDCS can also modulate blood flow (Zheng et al., 2011), neuronal synapsis strength, triggering plasticity process (Polania et al., 2011). Despite the fact that its mechanisms to ameliorate behavioral functions are not entirely understood, this technique has been proposed as an add-on therapeutic method in MS rehabilitation.

  To date, the most investigated symptomatic condition in studies with tDCS is fatigue. These studies have been performed with different protocols, including stimulation of bilateral motor cortex (Ferrucci et al., 2014), sense-motor cortex (Tecchio et al., 2014), or dorso-lateral prefrontal cortex (Saiote et al., 2014), and have shown a decrease in fatigue at the end of active stimulation. Regarding motor performance, it was observed that a single session of anodal tDCS on primary motor cortex M1 contralateral to the more restricted limb had increased corticospinal motor output and strength (Cuypers et al., 2013). Furthermore, it has been shown that anodal tDCS applied to the cerebellum can increase motor pattern learning (Galea et al., 2012) and, when combined with the performance of specific motor tasks, enhances the adaptation process. Indications of tDCS are also present for the treatment of chronic pain (Mori et al., 2010) and cognitive functioning, such as attention and speed of information processing (Mattioli et al., 2016).
- **Video Game Therapy (VGT)**. Is defined as the use of interactive simulations created with hardware and software to give to the individuals the opportunity to engage in virtual environments that are as realistic as possible (Weiss et al., 2006). It represents a recently introduced option for the rehabilitation of patients with neurological diseases to ensure continuity of rehabilitation or maintain its benefits after hospital discharge (Bonnechère et al., 2016). VGT integrates physical activity into a virtual reality and requires active body movements to control the gaming experience. Many technologies such as Nintendo Wii and Xbox Kinect have been adapted for this purpose (Perrochon et al., 2019). In clinical practice, therapists make use of so-called motor learning strategies (MLS), which are " observable therapeutic actions in which therapists consider task and client-specific factors to select and to apply evidence-based practice and feedback

variables for optimal motor learning" (Levac et al., 2011). VGT offers several advantages: real-time multisensory feedback, objective evaluation of progress, possibility to vary the task and make the treatment more engaging, suitability for home use, and low cost (Keshner & Fung, 2017; Porras et al., 2018, Perrochon et al., 2019). In addition, activities of daily living can be simulated in the virtual environment, which involves many dual-task situations. Our ability to predict the effectiveness of a motor response depends on the continuous calibration of internal models in the CNS that predict sensory consequences and modify our responses to errors through motor adaptation (Shadmehr et al., 2010). These internal models are distinguished into three groups by Miall and Wolpert (1996): forward model, external world behaviour model and inverse model. There is an intrinsic sensory mismatch between the feedback derived from our internal model of prediction and the visual and haptic feedback provided by the virtual environment. Essentially, our position in the virtual world does not reflect the spatial coordinates of our limbs at the end of the movement. This spatial mismatch is corrected by our CNS through motor learning to produce efficacious movement in the virtual world (Keshner & Fung, 2017). This type of training could induce a reorganization of neural architecture and stimulate the recovery of motor skills after neurological injury (You et al., 2005). Regarding its effect in the cognitive area, VGT showed positive effects on attention, visual and verbal memory, executive functions, and dual task; finally, it was shown to reduce cognitive-motor interference (Liao et al., 2019, Coyle et al., 2015, Mrakic-Sposta et al., 2018). Action video games are the typology that carries the greatest benefits for perceptual and attentional skills due to the speed of gameplay, the high input of perceptual, cognitive, and motor stimuli, the emphasis on peripheral processing of the visual field, the demand in terms of divided attention, the need to constantly make spatial and temporal predictions about future game events, and the continuous feedback (Green & Bavelier, 2012). Despite the positive effects of VGT mentioned above, other authors have reported limited effects and have recommended the need for further studies to demonstrate its efficacy and optimal frequency/intensity of intervention (Cano Porras et al., 2018; Perrochon et al., 2019).

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CHAPTER 2

STROKE

2.1 Definition and Epidemiology

The World Health Organisation (WHO) describe the term 'stroke' as "a clinical syndrome consisting of rapidly developing signs of focal or global disturbance of cerebral function lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin' (WHO 1978).
Differing from the classic definition of stroke, the newer forms include the various subtypes of stroke (Shakir & Norrving, 2017); however, the classic features in the definition remain the same, emphasizing acute focal neurological dysfunction. The full definitions included in the American Heart Association (Jauch et al., 2013) from the ICD-11 (approved by the 2015 World Health Assembly) are presented below:

- Cerebral Ischemic Stroke. Acute focal neurological dysfunction caused by focal infarction at single or multiple sites of the brain or retina. Evidence of acute infarction may come either from (a) Symptom duration lasting more than 24 hours (b) Neuroimaging or other technique in the clinically relevant area of the brain.
- Intracerebral haemorrhage. Acute neurological dysfunction caused by haemorrhage within the brain parenchyma or in the ventricular system.
- Subarachnoid haemorrhage. Acute neurological dysfunction caused by subarachnoid haemorrhage Stroke not known if ischemic or haemorrhagic.
- Acute focal neurological dysfunction lasting more than 24 hours (or lead to death in less than 24 hours), but a subtype of stroke (ischemic or haemorrhagic) has not been determined by neuroimaging or other techniques.

Stroke represent a major health problem worldwide. Low- and middle-income countries have been experiencing an increased incidence over the last years (Owolabi et al., 2018). However, is in high-income country that stroke constitutes the second cause of death and the third leading cause of disability (VL, 2017). Stroke is the second most common cause of death and a leading cause of adult disability in the European Union; it affects ≈1.1 million inhabitants of Europe every year and causes 440 000 deaths (Béjot et al., 2016; Mozaffarian et al., 2016). The cost connected with stroke was preventive at €45 billion, counting direct and indirect costs of care provision and productivity loss (Wilkins et al., 2017). Because populations persist to grow and live to an older age, stroke events and their long-term sequelae, and the associated costs, are provided to increase dramatically: the number of people living with stroke in the European Unionvis estimated to increase by 27% among 2017 and 2047. One of the most important consequences of the increased survival is the rising number of disabilities in adults. In fact, stroke is the third cause of disability-adjusted life-years (DALYs), causing significant physical, emotional, and cognitive disabilities among survivors (Johnson et al., 2019).
A reviews on stroke epidemiology in Italy enclosed a total population of 2 262 940 people, with a hospitalization rate from 82% to 98%. Annual incidence rates standardized to the Italian population ranged from 130/1 00 000 to 273/1 00 000 in women and from 175/1 00 000 to 360/1 00 000 in men. The mean age at stroke onset was 74,6 ± 1,1 years, 76,6 years in women and 72,3 years in men. Considering the type of strokes: 67,3–82,6% were classified ischemic, 9,9–19,6% as primary intracerebral haemorrhage, 1,6–4% as sub-arachnoid haemorrhage, and 1,2–17,7% as undetermined. Fatality rates at 30 days after stroke's event ranged from 18% to 33% while one-year case-fatality rates ranged from 38% to 40%.
These data from selected Italian registers denote the great burden of the disease on our national healthcare system. Thus, the accomplishment of preventive strategies, either population-based or addressed to the single patient at a high risk of stroke, is important to reduce the burden of the disease (Sacco et al., 2011).

2.2 Risk factors

The goal of the therapists is to recognise risk factors, and either minimise or with the help of the patient to avoid them. Concurrently with influencing the risk factors, it is known that all changes should be done systematically, consciously through self-empowerment and with professional help or with the help of close family. To prevent risk factors, medicaments and the change in lifestyle can be used.

There are two groups of risk factors (Seshadri & Debette; 2015):

- No-modifiable risk factors (that cannot be influenced): increasing age, having several genetic loci that give a predisposition, being women, being Afro-Americans ethnicity).
- Modifiable risk factors (that can be influenced): physical inactivity, smoke, alcohol and illicit substances abuse, sleep habits, diet rich in saturated fat, trans fat, cholesterol, sodium and calories, high blood pressure, both systolic and diastolic, hyperlipidaemia, carotid artery disease, peripheral artery disease, atrial fibrillation and other heart diseases (i.e., such as coronary heart disease, heart failure, dilated cardiomyopathy, heart valve disease and congenital heart defects).

In addition to these, there may be other factors linked to a higher stroke risk, such as geographic location, especially the southeaster countries, and socioeconomic factors such a lower income.

Finally, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), identifying as one of the neurological manifestations into the central nervous system (Lahiri & Ardila; 2020). A number of mechanisms are involved in stroke in SARS-CoV-2, including a hypercoagulable state, disseminated intravascular coagulation, necrotizing encephalopathy, vasculitis, and cardiomyopathy (Spence et al., 2020).

2.3 Pathophysiology

Stroke is defined as an abrupt neurological outburst caused by impaired perfusion through the blood vessels to the brain. Two main mechanisms might lead to stroke: ischaemia and haemorrhage.

Ischemic stroke

Ischemic stroke is caused by deficient blood and oxygen supply to the brain; it constitute at around 85% of casualties in stroke patients. Ischemic occlusion generates thrombotic and embolic conditions in the brain (Musuka et al., 2015). Specifically, in thrombosis, the blood flow is affected by narrowing of vessels due to atherosclerosis; the build-up of plaque will eventually constrict the vascular chamber and form clots, causing thrombotic stroke. While, in an embolic stroke, decreased blood flow to the brain region causes an embolism; the blood flow to the brain reduces, causing severe stress and untimely cell death (i.e. necrosis). Necrosis is followed by disruption of the plasma membrane, organelle swelling and leaking of cellular contents into extracellular space, and loss of neuronal function (Broughton et al., 2009). Other events that contribute to stroke are inflammation, excitotoxicity, free radical-mediated toxicity, cytokine-mediated cytotoxicity, oxidative stress and infiltration of leukocytes, complement activation, impairment of the blood–brain barrier, activation of glial cells, energy failure, loss of homeostasis, acidosis, increased intracellular calcium levels Qureshi et al., 2003; Wang et al., 2007; Suh et al., 2008; Gelderblom et al., 2009; Woodruff et al., 2011)

Haemorrhagic stroke

Haemorrhagic stroke is originate by bleeding or leaky blood vessels. Haemorrhagic stroke accounts for roughly 10–15% of all strokes and has a high mortality rate. In this case, stress in the brain tissue and internal injury cause blood vessels to rupture, this produces toxic effects in the vascular system, resulting in infarction (Flaherty et al., 2005). It is distinguishing into subarachnoid and intracerebral haemorrhage. In the latter, blood vessels rupture and cause abnormal accumulation of blood within the brain. The principal reasons are hypertension, disrupted vasculature and excessive use of anticoagulants and thrombolytic agents. In subarachnoid haemorrhage, instead, blood accumulates in the subarachnoid space of the brain due to a head injury or cerebral aneurysm (Testai & Aiyagari, 2008; Aronowski & Zhao, 2011).

2.4 Acute stroke

2.4.1 Clinical manifestations based on neurovascular anatomy

To comprehend the clinical manifestation of the stroke, it is important to consider the neurovascular anatomy. Signs and symptoms of stroke depend on the site affected by the loss of blood supply and on the extent of the lesion. The blood flow to the brain is managed by two internal carotids anteriorly and two vertebral arteries posteriorly; thus, the brain has a anastomotic circulation, called circle of Willis which provides constant and regular blood flow protecting the brain from ischemia and infarction. Sometimes anastomotic links among left, right, posterior, and anterior parts of the brain are not enough to protect it from vascular damage. Moreover, individual variations must be considered; some studies have shown how certain types of Willis's circle variation predispose people to cerebrovascular diseases, including cerebral aneurysms (Oumer et al., 2021).

Despite current advances in imaging methods to clinical practice, stroke still remain a clinical diagnosis characterized by the sudden onset of focal neurological deficits. The identification of clinical features of acute stroke is essential because it not only gives information about stroke location, but it also gives us information that is important for stroke aetiological investigation, prognosis, and treatment allocation. Patients and family members should be educated about stroke symptoms and the necessity for urgent evaluation. Indeed, the American Stroke Association is promoting the F.A.S.T. (face drooping, arm weakness, speech difficulty, time to call the rescue); almost 89% of patients would have sudden disruptions of face and arm movements and disturbance of speech. This improves patient knowledge about stroke and to expedite activation of rescue services (Kleindorfer et al., 2007). One of the most prominent stroke features is the abruptness in appearance of various types of local neurological deficits.

Albeit diverse clinical outcome can be observed in patients, some uniformity in signs/symptoms origin by stroke justifies the assignment of typical syndromes, depending on which artery was occluded and on the suffering area. A brief representation of each of the main syndromes is reported below (Adams and Victor's Principles of Neurology, XI Edition, 2019).

- Anterior Cerebral Artery (ACA) Stroke Syndrome. The ACA provides the anterior and upper part of the cerebral cortex. ACA stroke is constitute by transcortical motor aphasia, gait apraxia, contralateral weakness/sensory loss, affecting distal contralateral leg more than upper extremity, contralateral grasp reflex and paratonic rigidity.
- Middle Cerebral Artery (MCA) Stroke Syndrome. Cortical branches of the MCA supply 2/3 of the lateral surface of the hemisphere, including the parietal lobe and the superior part of the temporal lobe with the insula, the lateral and frontal lobe. Important areas of neurological specialization within the MCA territory include the primary motor and sensory areas for the face and upper extremity as Broca's and Wernicke's language areas in the dominant hemisphere. MCA stroke syndrome could lead to contralateral sensory loss, contralateral homonymous hemianopsia, contralateral hemiplegia/hemianesthesia. Visual perceptual deficits including left neglect can occur if the damage is right-sided, while aphasia can occur if left hemispheric is damaged.
- Posterior Cerebral Artery (PCA) Stroke Syndrome supplies the upper brainstem, the thalamus, parts of cerebellar peduncles, the infero-medial part of the temporal lobe and the medial part of the occipital lobe. The PCA stroke includes diverse syndromes depending on the occlusion site: Weber's syndrome associated with third cranial nerve palsy and contralateral pyramidal deficit; Claude's syndrome with third cranial nerve palsy and contralateral cerebellar ataxia; Benedikt's syndrome with third cranial nerve palsy and choreoathetosis, hemianesthesia or contralateral tremors; Nothnagel's syndrome with palsy of the third cranial nerve and hemiataxia, ptosis, and paresis of the superior rectus muscle; and Parinaud's syndrome that indicates involvement of the quadrigeminal plate.
- Lacunar Stroke. It occurs when small penetrating branches of the cerebral arteries become occluded. Therefore, the lesion following a lacunar stroke is smaller and often silent. Most lacunar infarcts occur within the deep grey nuclei and some may involve multiple sites (i.g. pons, thalamus, internal capsule and corona radiate, caudate). The most frequent form of lacunar stroke includes symptoms as hemiplegia of face, arm and leg, hemisensory deficit, clumsiness and mild weakness of the hand, dysarthria and dysphagia, and ipsilateral hemiparesis with ataxia.

2.4.2 Therapeutically and Pharmacological management

The stroke management involves the acute ischaemia solution and primary and secondary prevention. For the management of the acute phase, current guidelines strongly recommend intravenous thrombolysis, within 3 hours without ICH on computerized tomography (CT); it is also recommended between 3 and 4.5 hours in certain patients. The tissue plasminogen activators is the most used intravenous thrombolysis agent used in acute stroke. Intraarterial thrombectomy must be considered within 6 hours or within 16 hours in determined patients (Powers et al., 2018). Stroke risk decreases with the control of modifiable risk factors, that is with primary prevention. An example is the use of anticoagulants in patients with atrial fibrillation (Meschia et al., 2014). The role of aspirin in primary prevention remains unclear and controversial; to date, no evidence demonstrate the efficiency of aspirin in the cardiovascular disease prevention (Raber et al., 2019). Strategies to reduce the risk of early recurrence of ischaemic stroke, depending of patient, include immediate antiplatelet therapy and early carotid revascularisation. Aspirin, together with anticoagulants, is also efficient in long-term secondary prevention (Hankey, 2014). ICH management guidelines highly recommend the solution of underlying coagulopathies. Moreover, is recommend the rapid lowering of blood pressure below 140 mmHg. Surgical intervention has to be considered when the cerebral hypertension does not improve (Hemphill et al., 2015).

2.5 Consequences of stroke

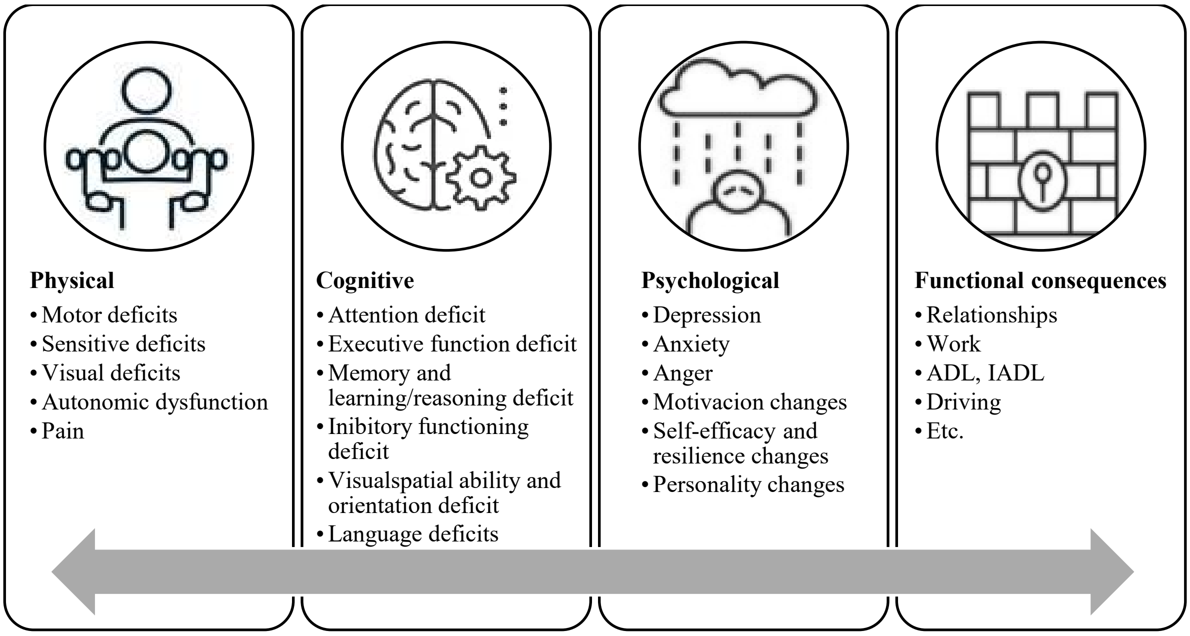

Figure 6. Consequences of stroke

2.5.1 Major clinical signs and symptoms

The impairments associated with a stroke exhibit a wide diversity of clinical signs and symptoms. Disability, which is multifactorial in its determination, varies according to the degree of neurological recovery, the site of the lesion, the patient's premorbid status and the environmental support systems. The main clinical consequences of stroke are reported below (Sinanović et al., 2011; Sand et al., 2013; Al-Qudah et al., 2015; Kessner et al., 2019).

Motor deficits

- Paralysis: the loss of the ability to move some or all of your body. Paralysis can affect any part of the body, and including the face, the hands, one arm or leg (monoplegia), one side of the body (hemiplegia).

- Paresis: is a condition where the muscles in an area of the body become weaker and difficult to move voluntarily.
- Ataxia: involves a lack of coordination and muscle control. It can occur after stroke and may affect various body parts including the eyes, hands, arms, legs, body or trunk, and speech. It is most common after a cerebellar stroke.

Sensitive deficits

Sensory loss across tactile, proprioceptive and higher-order sensory modalities such as deficits in two-point discrimination, stereognosis and graphesthesia are common after stroke, and may be associated with the degree of weakness and the degree of stroke severity.

- Hypoesthesia: partial loss of sensation
- Anaesthesia: total loss of sensation
- Paraesthesia: abnormal sensations perceived without specific stimulation.

Visual deficits

- Amaurosis: refers to an acute loss of vision eye, whether temporary or permanent
- Visual field deficits
    - Blindness
    - Bitemporal hemianopsia: describes the ocular defect that leads to impaired peripheral vision in the outer temporal halves of the visual field of each eye.
    - Homonymous hemianopia: involves vision loss on the same side of the visual field in both eyes.
    - Quadrant hemianopia: refers to an anopia affecting a quarter of the field of vision
    - Scotoma: a spot in the visual field in which vision is absent or deficient.
- Diplopia: double vision (due to oculomotor system impairment).

Language deficits

- Aphasia: loss or impairment of verbal communication. It can be classified in:
    - Nonfluent aphasias: Broca's, transcortical motor, global and mixed transcortical aphasia;
    - Fluent aphasias: anomic, conduction, Wernicke's, transcortical sensory, subcortical aphasia.
- Alexia: acquired inability to read. It can be classified in 3 categories: pure alexia with agraphia, pure alexia without agraphia, and alexia associated with aphasia.
- Agraphia: is defined as disruption of previously intact writing skills. Writing involves several elements: language processing, spelling, visual perception, visuospatial orientation for graphic symbols, motor planning, and motor control of writing. A disturbance of any of these processes can impair writing.
- Acalculia: is a clinical syndrome of acquired deficits in mathematical calculation, either mentally or with paper and pencil. There are three principal types of acalculia: acalculia associated with language disturbances (i.e. number paraphasia, number agraphia, or number alexia) and acalculia secondary to visuospatial dysfunction with malalignment of numbers and columns, and primary anarithmetria entailing disruption of the computation process.

Autonomic dysfunction

Autonomic dysfunction secondary to stroke is not limited to cardiovascular manifestations, as heart rate variability, abnormal heart rhythm and cardiac death, blood pressure variability, baroreflex sensitivity variability. Autonomic dysfunction extends to sudomotor, vasomotor, impotence, and urinary dysfunction.

Pain

Pain is a frequent issue in stroke survivors. For example, shoulder pain prevalence is reported to be between 9% and 40%; 79% of patient describe it as moderate-severe within 4 months of stroke onset

(Lindgren et al., 2007). Shoulder pain can accompany hand pain, delineating the shoulder-hand syndrome (SHS) with a prevalence arrives up to 70%. Several mechanisms are involved in shoulder pain and in SHS, such as spasticity and stiffness (Raghavan, 2015), inflammation and sympathetic disfunction (Pertoldi & Di Benedetto, 2005). Pain can affect different aspects of the upper limb rehabilitation; it can lead to learned non-use that can persist after the resolution of the pain (Raghavan, 2015). Moreover, patients who experience after-stroke pain assess their general health to be worse than patients without pain (Lindgren et al., 2007). Thus, pain could lead to mood alteration and shortage of motivation in the rehabilitation process; in general gets worse the quality of life.

2.5.2 Cognitive functioning

In stroke survivors, cognitive impairment occurs frequently. However, the cognitive profile of poststroke dementia is understandably complex, especially due to the heterogeneity of stroke and its effects on cerebral function. The prevalence of poststroke cognitive impairment varies for the difference between the countries, the races, and the diagnostic criteria. While poststroke cognitive impairment (PSCI) is mild in many stroke survivors, numerous studies have reported a prevalence of dementia in poststroke cases that varies from 7.4% in a population-based study of first stroke to 41.3% in hospital-based cases of recurrent stroke (Pendlebury & Rothwell, 2009). The risk of post-stroke cognitive impairment is connected to both vascular factors and the demographic factors (i.e. age, education and occupation). The underlying mechanisms of post-stroke cognitive impairment are not known in detail. Nevertheless, the neuroanatomical lesions caused by the stroke on strategic areas such as the hippocampus and the white matter lesions, the cerebral microbleeds due to the small cerebrovascular diseases and the mixed dementia with stroke, alone or in combination, contribute to the pathogenesis of post-stroke cognitive impairment (Sun et al., 2014). Strategic lesions can theoretically induce cognitive impairment of any kind, but the most frequently affected cognitive domains in stroke patients appear to be attention/ processing speed and frontal execution function (Hochstenbach et al., 2003; Sachdev et al., 2004). This is particularly the case early after stroke (i.e. first month), in which as many as 70% of stroke patients reportedly experience impairments in speed of information processing and attention (Hurford et al., 2013). In the cognitive domain of executive function, rule deduction and shifting are impaired in 20% to 30% of patients, verbal fluency and action speed are impaired in 33% to 60% (Tatemichi et al., 1994; Ballard et al., 2003; Rasquin et al., 2004). The few studies of the behavioural domain of executive function have focused on apathy, which was found in 20% to 40% of stroke patients (Angelelli et al., 2004; Brodaty et al., 2005; Mayo et al., 2009; Hama et al., 2011). Another common consequence of stroke is the syndrome of visuospatial neglect: a disorder of attention whereby patients characteristically fail to orientate, to report or to respond to stimuli located on the contralesional side. It is more severe and persistent following right hemisphere damage, with reported frequencies in the acute stage of up to 80% (Li & Malhotra, 2015). By contrast, visual and verbal memory may be the least affected domains following stroke, with impairments reportedly occurring in around 15% and 30% of stroke patients, respectively (Hurford et al., 2013). Albeit, some studies have found memory impairments existent in up to 60% if stroke patients, 3 months following stroke (Jokinen et al., 2015).

Interestingly, trajectories of recovery seem to vary by domain. It was found that the most prominent early impairments also demonstrated the greatest recovery potential. Specifically, impairments in attention and speed processing declined from 70% in the acute period to <40% at 3 months. This may suggest that, in many cases, existent memory impairments following stroke reflects underlying neurodegeneration that pre-dates the stroke (Hurford et al., 2013). However, research on domain specific recovery potential has been inconsistent. It was found that recovery was greatest in the domains of executive functioning, aphasia and long-term memory, whereas deficits in attention and short-term memory tended to persist (Lesniak et al., 2008). In contrast, another study found that prevalence of memory impairment declined from 23-55% at 3 months to 11- 31% at 1 year (Snaphaan & De Leeuw, 2007). Therefore, no firm conclusion can be drawn at present as to underlying nature of any given form of post-stroke cognitive impairment. Finally, anosognosia following stroke deserves attention, it is a self-awareness disorder which prevents brain-damaged patients from recognizing the presence or appreciate the severity of deficits in sensory, perceptual, motor, behavioural or cognitive functioning, which are evident to clinicians and caregivers. Anosognosia has gained importance for its striking phenomenology, its incidence in the stroke population and because it is detrimental to the recovery and rehabilitation course (Gialanella et al., 2005; Orfei et al., 2007).

Due to the importance of the role of cognitive functioning in rehabilitation, is necessary consider into the rehabilitation's package the cognitive rehabilitation. It involves "a systematic, functionally oriented service of therapeutic activities that is based on assessment and understanding of the patient's brain-behavioural deficits" (Cicerone et al., 2000). Various interventions aim to: 1) reinforce, strengthen or re-establish previously learned patterns of behaviour; 2) establish new patterns of cognitive activity through compensatory cognitive mechanisms for impaired neurological systems; 3) establish new patterns of activity through external compensatory mechanisms such as personal orthoses or environmental structuring and support; and 4) enable persons to adapt to their cognitive disability. Cognitive rehabilitation directs itself to several areas of cognition such as attention, concentration, perception, memory, comprehension, communication, reasoning, problem-solving, judgement, initiation, planning, self-monitoring and awareness (Cumming et al., 2013).

2.5.3 Psychological well-being

Stroke survivors often suffer from psychological distress and neuropsychiatric disorders. About a third of them suffer from depression, anxiety or apathy, which are the most common neuropsychiatric consequences of stroke. However, sometimes the diagnosis is not well defined and it may be more appropriate to identify individuals with the broader term of psychological distress to capture the complexity of the phenomenon and the intersection between diagnoses (Crowe et al., 2016). The neuropsychiatric consequences are disabling and can have a negative influence on recovery, reduce the quality of life and are a major source of stress for the caregiver. They are also more likely to be hospitalized and are more frequent users of health services. Stroke severity, stroke-related disabilities, cerebral small vessel disease, previous psychiatric illness, poor coping strategies, and unfavourable psychosocial environment affect the presence and severity of psychiatric sequelae of stroke. Despite the availability of screening tools and the growing evidence of the beneficial effects of available pharmacological and behavioural interventions, neuropsychiatric disorders attributed to stroke are currently underdiagnosed and undertreated (Ferro et al., 2016). Current interventions often focus only on the pharmacological management of psychological distress rather than on seeking the underlying factors that might be susceptible to psychological interventions.

Post – stroke depression

Following a stressful, unexpected and dramatic event such as stroke, transient feelings of sadness are a normal consequence and not a pathological reaction. However, about one third of patients develop a depressive disorder after the ictal episode, which can be found through two criteria: a prominent and persistent depressed mood and / or anhedonia, that is, a decreased interest or pleasure in activities that were previously enjoyable. Other symptoms such as loss of energy, decreased concentration, psychomotor retardation, decreased appetite and insomnia are also common; suicidal thoughts and guilty feelings may occur but are less common (Caeiro et al., 2006). Several studies show that depressive disorder associated with stroke increases patient mortality, especially in patients < 65 years. Moreover, it has a negative effect on functional recovery and quality of life, mainly in the emotional and social areas, increases the risk of institutionalization and is associated with an increased risk of anxiety and, more generally, with the onset of neuropsychological sequelae of another nature (Ayerbe et al., 2013). The main predictors of post stroke depression have long been researched, including factors closely related to the ictal event (i.e., large lesion volume, silent heart attacks, severity of neurological damage and associated disability), and predisposing factors related to the person (i.e. lack of social support, patient's lifestyle, personality, subjective experience of the stroke event, coping strategies ability) (Ferro et al., 2016). Despite the high prevalence of stroke-associated depressive disorder and the availability of treatments, depression remains underdiagnosed and undertreated; in fact, about 60% of patients do not receive an adequate diagnosis and are not treated adequately (Fuller-Thomson et al., 2012).

Anxiety disorders

The prevalence of anxiety following stroke is stable over time: 20% of patients manifest it within the first month, compared with 23% 1-5 months and 24% after 6 months. 25-50% of patients with acute anxiety after stroke develop permanent chronic anxiety and the concomitance of depression and anxiety increases the probability that the latter is chronic (Burton et al., 2013).
Panic attacks and phobias have been found, but the most common pathology is the generalized anxiety disorder (Ferro, 2013): a condition characterized by a constant anxiety state that leads to disproportionate and incongruous pervasive worries in different areas of patient's life. The predictive factors emerged for this disorder are: young age and female sex, previous diagnosis of depression or anxiety, alcohol abuse, aphasia, history of insomnia, cognitive impairment, impairment in activities of daily living and social functioning, inability to work, being single and living alone or not having social contacts (Ayerbe et al., 2014).

Post-traumatic stress disorder (PTSD)

Stroke is an unexpected event that places the patient in life threatening and causes serious disabilities, therefore it is often revived in an unpleasant and uncontrollable way. PTSD is characterized by intrusive symptoms such as memories, dreams and flashbacks of the event, persistent avoidance of stimuli associated with stroke, negative alterations in cognition and mood, increased reactivity with episodes of irritability, anger, exaggerated response to alarm. PTSD is found in 10% of patients, is more common in youngest, in women and in subjects with a low level of education. The risk is also greater in case of recurrent strokes, more severe disability, comorbidities including depression and anxiety, previous psychiatric disorders. The peritraumatic discomfort of the acute event is able to predict the symptoms of PTSD and also correlates with their intensity, although this correlation tends to decrease over time (Letamendia et al., 2012). PTSD negatively affects the patient's mental health and leads to a reduction in quality of life, it is also associated with a higher risk of treatment nonadherence (Kronish et al., 2012).

Personality changes

There are several types of personality changes in stroke patients grouping into 3 main groups by the DSM 5: A, B, C. These are: aggressive, disinhibited, paranoid, labile, and apathetic types; and represent a change from the individual's previous personality model.
Personality has a complex one-to-one relationship with stroke. Some personality traits, including type A, anger, pessimism, high extroversion, neuroticism increase the risk of stroke and influence the stroke outcome and the response to treatments. Conversely, the stroke itself can affect the personality. These changes are long-term, more marked and intense than those resulting from the association with other chronic diseases. Stroke is associated with a decrease in the "positive pole" of the domains of personality traits, including extroversion, emotional stability, awareness, and openness to experience. The prevalence of such stroke-related disorders is not well defined, in some studies they are defined as rare and are estimated to occur in less than 1% of stroke survivors, however other studies show a frequency of apathy of 37% (Jokela et al., 2014).
The two changes most frequently found in stroke patients are:

- *Apathy*
  Motivation disorder characterized by reduced physical and mental activity and emotional indifference. It is expressed by greatly reduced motor, behavioural skills and of verbal initiative, a lack of interest in previous activities and hobbies, and a preference for passive activities. In general, patients with post-stroke apathy show little improvement over time (Van Almenkerk et al., 2015). The chronic-persistent form is associated with cognitive impairment, functional deficits, depression, recurrent strokes and suicide. Apathy therefore interferes with rehabilitation and compromises the health-related quality of life.

- *Aggressiveness*
  In the first acute phase, the failure of inhibitory behavioural control is probably the main cause of aggressive behaviour, and the hospital environment can also be perceived as hostile or

humiliating, thus contributing to the development of such behaviour. Chronically, the three components of anger (emotional, cognitive and behavioural), the subjective experience of anger and the behaviour associated with anger can be dissociated. Therefore, subjects can behave aggressively without getting angry or, conversely, feel only hostility without showing aggressive behaviour. Anger and/or aggression can be secondary to the loss of empathy, or can be symptoms of various neuropsychiatric disorders, including delirium, mania, psychosis, vascular cognitive impairment and catastrophic reactions (Ferro, 2013).

Suicide

Although the rate is higher in stroke patients than in the general population, suicide is still rare after stroke. Suicidal thoughts can develop soon after the acute event but are more often observed in a delayed phase. They are particularly common in patients with low education, previous mood disorder associated with stroke (i.e. depression), young age, functional limitations, insomnia, pain, apathy (Pompili et al., 2012).

Bipolar disorders

Manic episodes and bipolar disorder are rare psychological complications of stroke, represent 1–2% of survivors. The attribution of these disorders to the acute event must be made only in cases where the onset of mania coinciding with or following the stroke: this can occur in conjunction with the acute event or following it in terms of days, months or years. Patient with stroke-associated mania may experience recurrent episodes of mania or bipolar disorder, that is, a disease characterized by alternating bouts of depression and mania. The most common clinical manifestations are: heightened mood, hyperactivity, talkative and insomnia or decreased need for sleep, as well as irritability, flight of ideas, grandiosity, lack of intuition and social disinhibition. Mania is more common after an injury to the right hemisphere (Santos et al., 2011).

Fear

This condition is more frequently and occurs mainly due to two factors: the awareness of mortality caused by the stroke, which leads the patient to experience the post-stroke time as 'borrowed time', and the suddenness of the acute event. The latter, unlike other chronic pathologies, denies to the individual the opportunity to adapt and to integrate the disease into personal life; usually, the patient not being physically or mentally ready, often feels vulnerable to a new acute event. Stroke, therefore, triggers a "fear of the unknown" which leads to a constant unpleasant feeling of anguish. Also, patients himself show contempt and criticism about own feeling of fear and the perceived inadequacy to explain it, face it and overcome it. There is evidence about the reciprocal relationship between patients' acceptance of stroke and their ability not to feel overwhelmed by fear and face the event (Crowe et al., 2016).

Loss of Self

Patients perceive stroke as a "rupture event" that determines a split in their identity: on the one hand the loss of self prior to the event, on the other, the rejection of the new identity and the desire to reacquire the previous one. Often, at the base of the refusal of the new identity, there is a lack of self-compassion, a fundamental process to allow acceptance of the natural changes resulting from event. Obstacles to returning one's identity are detected also into loss of energy and youth. Furthermore, the inconsistency between apparent physical health, if present, and psychological well-being, accentuate the discomfort. Indeed, the patient has the perception that only physical difficulties, and not psychological ones, can be tolerated and accepted. Thus, can be useful helping in the development of a self-compassionate mindset to reducing ongoing discomfort (Crowe et al., 2016).

Sense of loneliness and isolation

The social isolation is a fundamental component of the psychological distress experienced by the patient. It is perceived from two perspectives: an internal and an external loneliness. The first is associated with living psychologically alone with the stroke experience, the need to protect oneself and others from distressing thoughts and feelings. Patients are also often unable to communicate the perceived psychological impact of the event to others. While, the external loneliness is associated with new mandatory life circumstances, the loss of previous roles, isolation from others. Often, patient's psychological distress is compounded by having to deal with stroke without previous levels of social support. In this context, discharge from hospital and rehabilitation services was frequently experienced not as an indicator of improvement, but as an interruption of available help (Crowe et al., 2016).

2.5.4 Quality-of-life

The progress made in terms of acute treatment of stroke and rehabilitation of the first months have determined a significant increase in survival. Proportionally, the prevalence of stroke has therefore increase with an increasingly large slice of the population lives with stroke outcomes. This event produces chronic neurological disability that can substantially and permanently change the patients' live. The residual deficits that can be experienced after stroke, including those of a physical, sensory, cognitive, perceptual, communicative and emotional nature, have been extensively described. It has been emphasized how these deficits can affect a person's ability to maintain good functioning in activity of daily living and assuming the desired roles (Lau et al., 2003). Many people don't fully recover after stroke, thus their condition can negatively impact their life even many years after the event. Increment of stroke survival with a current demographic trends towards aging, have also led to an increasing focus on chronic diseases and to debilitating outcomes of acute diseases. Finally, last but not least, in recent decades there has been a change in the model of care, in particular a shift of the focus in healthcare from a traditional medical model, which viewed patients simply as biological organs, to a vision more human, i.e. we have moved on to consider the patient in a global way, considering his centrality, his role and his subjectivity (Mar et al., 2015). This also following the new definition of the concept of health given by the WHO in 1948 which defines it as "A state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”. Therefore, health no longer coincides only with the absence of physical illness, it is not something that one owns or does not possess, but a state within a continuum.

The direct evolution of the new concept of health is the quality of life (QoL). Quality of life is defined by the dedicated group of the World Health Organization (WHOQOL) as “individuals' perception of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns” (Whoqol Group, 1998). QoL is therefore a multidimensional concept that includes both the objective dimension, i.e. the healthy aspects, and the subjective one, i.e. non-medical aspects such as economic conditions, accommodation, cultural and religious factors, subject's perception. All these determinants are interrelated and the QoL experience for each patient is unique and dynamic, in fact it can vary relating to time and to personal and/or environmental factors. The goal of the treatment is not only to prolong the years of life, but to ensure that these years are characterized by adequate QoL. After an acute event, a more specific parameter is HRQoL (Health Related Quality of Life) which assesses the health-related quality of life. In stroke survivors, the mean scores of this parameter range between 0.47 and 0.68 (death equals 0 and complete health equals 1) and is less than the mean value for a healthy reference population (score 0.93) (Visser et al., 2014). It follows that quality of life of stroke survivors has become a focal point for healthcare professionals and researchers, it is considered the most relevant endpoint and outcome measure and increasingly a primary goal.

2.6 Upper Limb Motor Impairment

Sensorimotor impairment is the major obstacle after stroke (Wagner et al., 2007). The impairment can lead to functional limitation of the affected limb. The first step to provide appropriate and efficient treatments is the comprehension of the impairments underlying the motor limitation. The main functional consequences of stroke are: 1) learned non-use, 2) learned bad-use, 3) forgetting (Raghavan, 2015).

2.6.1 Learned non-use

At the beginning, the non-use is due to weakness or paralysis of the upper limb and sensory impairment. However, as the time passes, patients learn to not use the limb and the non-use may become a habit. Although patients can move the upper limb, they do not incorporate it in daily functional activities. Several conditions following stroke can direct to limited movements or immobility of the impaired limb. Weakness and paralysis mostly originate from the lack of cortex impulses to muscles, resulting in a belated contraction. The delayed initiation and termination of contraction mirror the motor function impairment and consequently the difficulties in daily activities (Chae et al., 2002). An electromyography study related slowness in contraction to weakness of the upper limb at 6 weeks after stroke (Canning et al., 1999). Mercier et al. (2004) provided evidence that sensory impairment can lead to motor disfunctions. In a task of matching force magnitude between the two arms, the lack of force perception and the presence of proprioceptive impairments contribute to the failure of the task.

2.6.2 Learned bad-use

It is well documented the co-activation of antagonist muscles in stroke patients during voluntary movement (Kamper & Rymer, 2001). Both the quality and the quantity of motor synergies of stroke survivors are affected by motor impairment, resulting in alteration of coordination (Pan et al., 2018). Another common aspect of motor impairment is hypertonicity, that can contribute to twist motor patterns and to limit motor activation (Marciniak, 2011). Weakness, paralysis, stiffness, spasticity, and sensory loss may alter the way of moving the limb, which, consequently, do not appear normal. Therefore, patients generete compensatory movements. The repetition of such altered movements let the patient store them, learning modified motor synergies. Hence, the performance will decline despite the training.

2.6.3 Forgetting

Rehabilitation based on motor learning should lead to structural reorganization of the injured brain area. However, due to the heterogeneity of results, it is still unclear whether such changes are beneficial to patients with stroke and whether motor rehabilitation actually produces those changes (Sampaio-Baptista et al., 2018). It was demonstrated that breaks during rehabilitation after stroke might be damaging; the declining performance in those cases might be due to forgetting of the previously learned limb motor functions (Krakauer, 2006). The underlying processes could be the lack of sensorimotor adaptation and the stop of repetition, i.e. the main mechanisms through which new motor skills are learned. Also, has been hypothesized an active process of unlearning, instead of forgetting. During a period of no-rehabilitation, some movements could be in competition, leading to an elimination of previously reinforced movements or to a substitution of them with others (Kitago et al., 2013).

2.7 Clinical evaluation

Over the past decades, there has been a gradual shift from a biomedical towards a more biopsycho-social model in rehabilitation medicine (Wade, 2016). The International Classification of Impairments, Disability, and Handicaps (ICIDH) and subsequently the International Classification of Functioning, Disability and Health (ICF) indicated the possible levels of patient assessment: structural and functional damage (Impairment), restriction of activity (Activity limitation) and participation (Participation restriction). In outpatient clinics there is increasing interest in, and emphasis on, measuring participation (Post et al., 2012) understood as the patient's involvement in everyday social situations through meaningful activities in the community, family and work. Participation restriction is frequent following stroke and significantly affects quality of life; thus, it is consider a key area in rehabilitation (Dijkers, 2010; Heinemann et al., 2011). The definition of impairment implies the assessment of anatomical damage through clinical and instrumental methods with the aid of neuroimaging and neurophysiology. It includes the identification of any comorbid pathologies and complications related to patient immobilization such as infections and bedsores. It also outlines the functional impairment resulting from the disease through specific assessment scales for cognitive, sensorimotor and musculoskeletal functions. During the physiatrist evaluation, the examination of the range of motion (ROM) measure the movement and associated pain around a specific joint or body part. Muscle trophism, osteotendinous reflexes and sensitivity are also assessed. Sensory impairment is a negative prognostic factor in the outcome of motor recovery and its evaluation focuses on the tactile, kinaesthetic and proprioceptive modalities, the most frequently affected in the cerebrovascular event; the judgments being normal-compromised or absent.

The physiatrist examination uses specific assessment scales to measure the individual signs and symptoms of stroke through graded scores which, repeated over time, quantify the patient's recovery profile and indicate the benefits of the rehabilitation treatment (Basaglia, 2009). First, to assess the severity of stroke through global assessment of deficits post stroke, there is the National Institutes of Health Stroke Scale (NIHSS). It is the most widely used deficit rating scale in modern neurology; it consists of 11 items; 2 items are passive range of motion (PROM) assessments delivered by a clinician. The other 9 items are visual exams conducted by the clinician. Each item is then scored on a 3-point scale (0=normal, 2=minimal function or awareness). NIHSS is consider a strong predictor of outcome and it is also widely used in emergency situations as its administration takes about 10 minutes. The NIHSS includes the following domains: level of consciousness, eye movements, integrity of visual fields, facial movements, arm and leg muscle strength, sensation, coordination, language, speech and neglect (Ortiz & Sacco, 2007). However, pursuing not only the patient's physical, but also social and mental well-being is an important goal that is part of the rehabilitation program to optimize its effectiveness (Elloker & Rhoda, 2018).

Other specific tests most used in the pathology of stroke are named below. It was divided the tests into sebsections: motor function, dexterity, spasticity, ADL and quality of life.

Motor function

- Fugl-Meyer Motor Assessment Scale (FMA): it is the gold standard for the clinical monitoring of motor recovery. It evaluate sensorimotor impairments in more detail by analyzing the dysfunctions in all their complexity. The FMA scale is divided into specific areas for the upper limb (FMA Upper Limb) and lower (FMA Lower Limb). Specifically, FMA-UE consists of four categories: Shoulder/Elbow/Forearm, Wrist, Hand/Finger, Coordination. It analyses the domains of motor, sensory, balance, joint movement and joint pain, each through multiple items evaluated with an ordinal scale of 3 points, from 0 to 2, in which 2 corresponds to the complete execution of the task. The higher the result, the more the performance approaches normal. The maximum score is 66 for the upper limb and 34 for the lower limb. Its introduction in the evaluation of the brain-injured patient has added particular value to the purely quantitative analyzes, introducing the analysis of the evolution of motor recovery that occurs under the influence of pathological synergies (Fugl-Meyer et al., 1975; Gladstone et al. al., 2002).
- Action Reserch Arm Test (ARAT): is a measure of upper extremity function and dexterity. It consists of 19 items designed to assess four areas of function ranging from grasping and gripping to pinch and gross movement. Each question is scored on an ordinal scale ranging from 0 (no movement) to 3 (normal performance of the task) (McDonnell, 2008).
- Wolf Motor Function Test (WMFT): provides a measure of upper limb ability and consists of 17 tasks subdivided into 3 areas: functional tasks, measures of strength, and quality of movement. Patients are scored on a 6-point scale (1=cannot complete task, 6=completes task as well as the unaffected side). The latter, as ARAT, are more useful in the assessment of chronic stroke, while in the acute and subacute phase the primary use of the FMA is recommended (Bushnell et al., 2015).
- Motricity Index (MI): measure strength in upper and lower extremities. The weighted score based on the ordinal 6 point scale (3 for the arm, 3 for the leg) (Demeurisse et al., 1980).
- Trunk Control Test (TCT): examines four axial movements. The scoring is as follows: 0, unable to perform movement without assistance; 12, able to perform movement but in an abnormal manner; and 25, able to complete movement normally (Verheyden et al., 2007).

Dexterity

- Box and Blocks Test (BBT): is used to measure the gross manual dexterity. It consists of moving as many small wooden blocks as possible, from one compartment to the other. The total number of blocks is 150 and patients have to move them in 60 seconds (Hsiao et al., 2013).
- Purdue Pegboard Test (PPT): is used to measure unimanual and bimanual finger and hand dexterity. Patients have to place in 30 secs as many pins as they can onto the pegboard, and then repeat this exercise for the other hand. Scoring depends on the number of pins they can place onto the pegboard in the given time (Toluee Achacheluee et al., 2016).
- Nine Hole Peg Test (9HPT) is used to measure finger dexterity. It consists of taking 9 pegs out of a container, insert them into the pegboard and, then, take them out and place again in the container as quick as possible, so a faster time corresponds a better outcome (Jobbágy et al., 2018).

Spasticity

- Ashworth Scale (AS) is used to evaluate the resistance and spasticity (or catch) in the joint during passive movement. The measure contains 15 functional movements done with the guidance of a clinician. These movements are divided into upper extremity and lower extremity. Each movement is then rated on a 5-point scale (the higher the score, the greater the spasticity) (Chen et al., 2019).
- Modified Ashworth Scale (mAS): it is similar to the previous but it contains 20 functional movements and the scoring range is on a 6-point scale (Charalambous, 2014).

ADLs

- Barthel Index (BI): measure the ability to carried out primary daily activities. It consists of a 10-item scale (activity of daily living such as feeding, bathing, grooming, dressing, bowel control, bladder control, toileting, chair transfer, ambulation and stair climbing). Each task is measured on a 3-point functional ability level of independence scale. Modified-Barthel Index (MBI) differs from original BI because has a 5-point rating scale. The total score indicates the patient's degree of autonomy, predicting length of stay and probability of discharge (Quinn et al., 2011).
- Motor Assessment Scale (MAS): is a performance-based scale used to assess everyday motor functions from basic gross motor upper and lower extremity to fine hand motor function. It consists of 8 motor-function based tasks measured on a 7-point scale (0=suboptimal motor performance, 6=optimal motor performance) (Carr et al., 1995).
- Functional Independence Measure (FIM): is an ordinal scale that measure the ability to carry out everyday tasks safely and without assistance. It can be subdivided into a 13-item motor subscale (mot FIM) and a 5 item cognitive subscale (cognFIM). There are 6 areas of function: bladder management, self-care, mobility, locomotion, communication, and social cognition. Each task is scored on a 7-point Linkert scale (1=total dependence, 7= total independence). It is a proven assessment method in the rehabilitation field as a care planning tool for its prediction of the necessary care load and the possibility of returning home (Heinemann et al., 1994).

Quality of life

- Stroke impact scale (SIS): offers a multidimensional measurement of consequences of stroke in multiple domains. It is a self-report questionnaire developed from the perspective and input of both the patient / caregiver and the experienced healthcare professional for the assessment of disability and health-related quality of life (HRQoL); that is, a measure to patient perceived impact following stroke. Stroke Impact Scale 2.0 consists of 59 items grouped into 8 domains, four of which are dedicated to the consequences of motor dysfunction of the upper limb: These are: strength, memory, emotion, communication, ADL / IADL, mobility, hand function, social participation, plus an item that evaluates the overall recovery of stroke (Vellone et al., 2015).

2.8 Predictors for post-stroke outcome

An ordinary practice in stroke-patients' assessment and a potentially crucial aspect of the rehabilitation program has become the motor outcome prediction. Indeed, prediction of motor function recovery during the acute and sub-acute phase of stroke could be useful for classify the patients, distinguishing those with a good or poor functional outcome at the end of rehabilitation. This distinction might help individualise the treatment thus resulting more efficacy. Since it is not yet clear which is the best rehabilitation approach for motor deficit of the upper limb, the effectiveness of rehabilitation varies significantly from each patient. It is believed that, to maximize the effectiveness of each rehabilitation technique, it is necessary to identify the target population to which the treatment should be addressed, stratifying patients based of characteristic biomarkers that inform about the possibility of deriving significant benefits from specific treatment. The clinical assessment of the upper limb impairment is one of the most strongly measures associated with motor function recovery, indeed, greater initial impairment is associated with poorer motor outcome (Coupar et al., 2012; Stinear, 2017). Other parameters have been shown to be predictive of negative outcome: advanced age, sphincter incontinence, severe paralysis, visuospatial deficits, history of previous strokes, poor trunk control (Basaglia, 2009). Several studies have indicated some clinical parameters as strongly predictive of motor recovery, i.e. age, type and size of lesion, time elapsed since stroke, motor function and neuroimaging findings (including cortical activation, network connectivity, and structural integrity) (Stinear, 2010; Quinlan et al., 2015).

For instance, the motor network connectivity measured with functional magnetic resonance imaging (fMRI) has been shown to facilitate individualized prediction of 86% accuracy (Rehme et al., 2015). A correlation between MRI features and proximal motor deficits was establish in other imaging studies. A greater asymmetry early determined between the lesioned side and the non-lesioned side of corticospinal tract significantly correlate with motor function outcome after 2 years from stroke onset; this demonstrate that the integrity of white matter correlated with functional outcome more strongly than the size of the damage (Puig et al., 2013). Furthermore, it also was found a weak correlation between imaging of corticospinal tract and FMA assessment 3 months after stroke onset (Doughty et al., 2017). Functional Magnetic Resonance Imaging (fMRI) during upper limb active movements showed that patients with greater activation of ipsilesional primary motor cortex, premotor cortex and contralesional cerebellum had a better motor outcome (Rehme et al., 2015). Therefore, there are different types of biomarkers, diagnostic, prognostic, outcome and predictive, of a clinical nature or deriving from neuroimaging.

However, the challenge is to identify neurophysiological biomarkers, considered the most indicative in the description of the complex mechanisms underlying motor recovery. Transcranial Magnetic Stimulation (TMS) allows to measure motor-evoked potentials (MEPs) by giving a magnetic stimulus on the contralateral primary motor cortex. The MEP that follows the excitation of the ipsilesional motor cortex reflects the integrity of the corticospinal tract and this is the very prognostic feature of TMS. In general, MEPs is a robust predictor of motor improvement, as shown by several studies (Stinear, 2017). However, it is also important specifying that, although the presence of MEPs is a good predictor of motor recovery, the literature reported a non-optimal negative predictive value of MEPs. Therefore, the absence of MEPs does not necessarily predict a poor motor outcome (Pizzi et al., 2009).

To date, exist an algorithm, called Predict Recovery Potential 2 (PREP2), which seems to predict motor outcome only considering clinical measures and the presence/absence of MEPs. It is possible that the PREP2 increase rehabilitation efficiency after stroke (Stinear et al., 2017a) and predicit functional outcome from 3 months to 2 years post-stroke (Smith et al., 2019). The electroencephalography (EEG) is another potential neurophysiological tool that might reveal specific activities of the brain after stroke. For example, delta power strongly correlated with the NIHSS scores after 30 days from acute event and the prognostic meaning of the EEG was significantly better than Magnetic Resonance Imaging (MRI) (Finnigan et al., 2004). Moreover, polymorphic delta activity and depression of alpha or beta power in the ischaemic hemisphere predicted poorer functional outcome, whereas the absence of slow activity with minimal decrease in background frequencies was prognostic for good outcome (Jordan, 2004). Also, a higher ratio between delta and alpha power correlated with poor functional recovery after neurorehabilitation (Leon-Carrion et al., 2009).

Unfortunately, none of the biomarkers have been implemented into clinical practice to individually guide the rehabilitation, maybe due to the big heterogeneity of available results.

2.9 Rehabilitation of the Upper Limb Motor Function

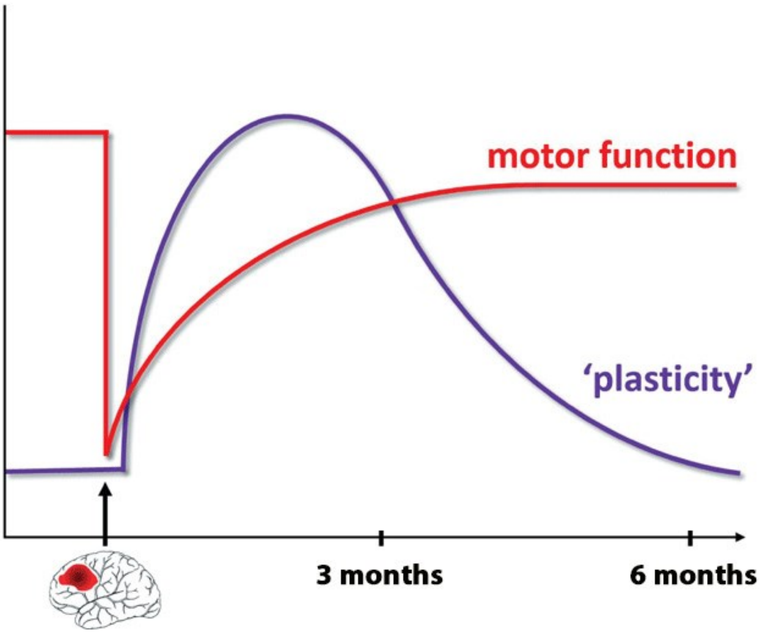

Figure 7. Trends in motor recovery and neuroplasticity after stroke (Hatem et al., 2016)

Most patients show some degree of spontaneous recovery, but this is generally incomplete. The recovery of motor skills following a stroke follows a natural pattern that can be changed by targeted intensive exercises (Schneider et al., 2016), especially if this practice begins within the first six months from stroke onset. The cure of stroke survivors today provides a rehabilitation intervention individualized to the patient and based on the knowledge of neural processes related to motor recovery. Several approaches of such restorative therapies exist, some of these are described below. Frequently, these are administered concurrently a conventional treatment or to alternative treatment, since their effectiveness can be related to different aspects of impairment.

Therapeutic exercise is a key factor in determining cortical plasticity since it is able to growing somatosensory inputs of the upper limb. There are two main factors to consider in rehabilitation after brain injury: the repetitive practice and specificity of activities. Regarding the first point, it is know that lack of movement leads to a loss of motor skills while post-stroke rehabilitation promotes motor reorganization. Therefore, it is one of the variables that significantly affects learning ability is intense repetition, be this physical or of other nature. About the task-specificity it is know that functional relevance of the gesture is required for motor learning to occur. Thus, repetition without a goal is often not enough for cortical relearning. Long-lasting cortical reorganization of specific areas can be achieved only with task-specific training.

- **Strength Training**. This type of therapy is featured by targeted active exercises against resistance. It centres on improving mainly range of motion, but not on spasticity or dexterity.
- **Constraint-Induced Movement Therapy**. Stroke survivors may adapt rapidly to non-use of the affected upper extremity, this therapy overcomes this effect promoting neuroplasticity and use-dependent cortical reorganization. The patient is constrained forcing to use the affected upper limb than one the unaffected.
- **Bilateral Activity Therapy.** Patient are asked to perform all activities with both upper limbs at the same time. The justification is that executing bilateral movements may activate the intact hemisphere and hence to make easy the activation of the damaged hemisphere.

- **Robot Assisted Therapy.** Robotic devices can be used to assist the patient in different situations. For example, the robot can be implicated in passive range of motion to help to maintain range and flexibility, to reduce hypertonia or resistance to passive movement. Furthermore, robot can also assist patients with active movements if the patient is not completely independent. Indeed, there are two types of robotic devices used for motor training: end-effector devices and exoskeleton devices. These robots give direct control of individual joints which can minimise abnormal movement or posture (Chang et al., 2013).
- **Virtual Reality.** It is not a therapy but a way to present stimuli, it consents to experience and interact with three-dimensional environments that could seem more ecological. Simulators includes head-mounted displays, computer or projector screens. This technique exploits the implicit learning (i.e. the subject is not aware of what he is acquiring with practice) that leads to improved motor performance. The advantages of using virtual reality within the rehabilitation program is to create an engaging and fun learning experience that motivates the patient join the possibility to personalize the training program.
- **Brain Stimulation.** The most used types of brain stimulation in rehabilitation comprehend transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS). The latter consists of delivering a single pulse or paired pulses or repetitive trains of stimulation: high frequency stimulation facilitates or suppress targeted brain regions. In tDCS, instead, mild electrical currents (1-2 mA) is applied to the primary motor cortex (M1) through two surface electrodes, one of these is placed over M1 and one other over the contralateral supraorbital region (Hummel et al., 2006).
- **Functional Electrical Stimulation** (FES). A treatment applies small electrical charges to a muscle that has become paralysed or weakened producing muscle contraction by stimulating motor axons. FES is utilized to reduce pain and spasticity, in general to ameliorate motor recovery (Alon et al.,2007).

Task-oriented training strategies demand some degree of voluntary movement, and are hence not applicable for people with severe stroke paresis. Since also cognitive-perceptual acts plays a pivotal role in re-learning motor skills, another possible intervention for the rehabilitation of upper limb is being across mental/cognitive stimulation.

- **Mirror Therapy.** Widely used in phantom limb pain. In this therapy a mirror is placed in patient's mid-sagittal plane, in this way movements of the non-paretic side are reflected as if it was the affected side; this form of visual imagery helps involving premotor cortex which is fundamental for neuroplasticity (Yazuver et al., 2008).
- **Motor Imagery**, i.e. mental practice of tasks. The individual imagines himself performing a particular action trying to perceive the kinaesthetic experience of movement. Significant effects have recently been obtained in stroke motor recovery as it has been found that during the imagery of the movement the same motor representations that are activated during the execution of the action and during its observation are recalled. Its efficacy derive to the fact that stored motor plans for executing movements can be accessed and reinforced without the active involvement of the injured limb (Stevens et al., 2003).

Also, pharmacological intervention can be used to manage plasticity by use of neuromodulators and molecules that improve synaptic efficacy and long-term potentiation or activate gene expression for growth of dendritic sprouts and spines (Dobkin et al., 2004). Pharmacological treatment can also be used to reduce spasticity, pain or to improve psychological well-being after stroke, i.e., to reduce anxiety and depression symptomatology.

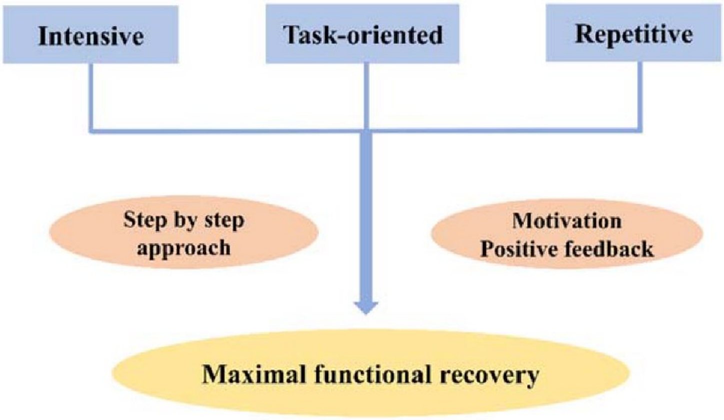

Figure 8. Approaches to promote neural plasticity (Kim et al., 2020)

2.9.1 Action Observation Training

Action Observation Therapy (AOT) is enclosed in rehabilitation cognitive strategies; recognizing its high potential to enhance motor recovery in stroke survivors, as the paretic arm functioning (Buccino et al., 2006; Ertelt et al., 2007; Garrison et al., 2010; Sarasso et al., 2015). It is a safe, simple rehabilitation technique that does not demand expensive equipment or constant supervision by the therapist. This intervention is characterized by observation a motor task performed by a healthy subject in person or up video, followed (or not) by the execution of the same task. Considering the videos as stimuli, it was proved that first person perspective is the best to enhance embodiment (Fu et al.,2014; Drew et al., 2015; Angelini et al., 2018). Regarding the type of stimuli to use, for humans, it would appear that there are no differences in cortico-spinal activation between observations of transitive and intransitive actions (Fadiga et al., 1995; and Maeda et al., 2002).

AOT based on the evidence that active and kinaesthetic movement experiences share the same neuronal networks activated during movement planning, preparation and execution. It follows that motor areas can be recruited not only when actions are actually performed but also when they are mentally exercised or just observed. Action observation is an approach that employs the Mirror Neural System (MNS), which is noted to operate both when performing a specific goal directed gesture and when this action is observed but not executing (Fadiga et al., 1995). Considering the neurophysiological perspective, it induces specific motor facilitation in the corticospinal system that increases the excitability of the injured sensorimotor system in the primary motor cortex facilitating the reorganisation of the brain in patients by activating central representations of actions through the MNS (Celnik et al., 2008). An important neural correlate of the coupling between action execution and perception, that reflect MNS, is Mu rhythm desynchronization, a field oscillation in the ∼10Hz range over the sensorimotor cortex (Stefan et al., 2005).

Understanding the networks involved in action simulation and their relationship to the areas recruited during actual movement execution is the core of neurorehabilitation, that uses these concepts to activate the neural circuits implicate in movement execution. Motor imagery, action observation and movement execution share some common networks, principally three areas: premotor, sensorimotor and parietal. The parietal premotor area interacts with the primary motor cortex (M1) for the precise coordination of the hand during grasping, while the dorsal premotor area contributes to the execution of the movement by operating the selection of the action. The sensorimotor area is liable for the transformation of theoretical rules into actions and non-motor cognitive processes. The parietal area is entailed in movement and in multisensory information processing, especially regarding the processing of tactile information, with a central role in the objects' use. Highlighting the importance of action perception in neurorehabilitation, AOT supplies an extension of classic therapeutic procedures for stroke recovery. In fact, it may represent an alternative vehicle of readjusting damaged but not completely lost circuits; offers the possibility to activate specific cortical areas and facilitates the activation of the damaged ones, preventing changes in cortical reorganization that occur after inactivity; it resulting an improve of upper limb functional dexterity. The advantage consist of AO can start earlier than conventional therapy in subacute patients when they are not able to perform any movement because of neural damages or pain.

AOT represent a novel tool to recover damaged cerebral networks of subjects with lesions of the central nervous system, according to different studies investigating efficacy of this therapy in patient both in chronic (Ertelt et al., 2007; Harmsen et al., 2015) and subacute stroke (Franceschini et al., 2012; Sale et al., 2014). AOT is used also in Parkinson's disease (Pelosin et al.,2010; Pelosin et al, 2013), children cerebral palsy (Sgandurra et al., 2013; Buccino et al, 2012) and in some orthopaedic illness (Bellelli et al., 2010; Park et al.; 2014). The role of AOT in stroke patients with hemiparesis or hemiplegia has been widely explored. However, some results of studies that explored the effectiveness AOT in stroke survivors are sometimes controversial.

AOT can be used simultaneously with other rehabilitation treatment, it has been showed that it facilitates motor learning and helps creating motor memory, moreover, motor improvements are kept after few months in contrast to motor training alone (Lee et al., 2013). A study compared the effects of the classical AOT which includes observation and imitation with observation alone or execution alone and a control group, which did none of the tasks; the observed-performed task was the act of drinking. Results displayed that all the experimental groups improved upper limb functional dexterity compare to the control group, and that classical AOT group functions were better that the other two experimental groups (Lee et al., 2013). A recent systematic review disclosed a strong evidence supports the benefits of AOT in hemiparetic stroke patients in improving the upper limb function and manual dexterity, measured by FMA, BBT and BI (Ryan et al., 2021). On the other hand, another systematic review drafted by Cochrane Stroke Group considered AOT to be only moderately beneficial for the upper limb motor function and for independence in ADLs. Indeed, enhancement in upper limb function did not appear to be clinically significant, and the evidence quality provided by the bulk of studies is low. Therefore, they considered the benefits provided by AOT for the upper limb motor recovery to be only limited (Borges et al., 2018). However, it is worthy to analyse the most prominent studies that assessed the efficiency of AOT in stroke rehabilitation. Stroke patients with motor deficits benefitted from combining observation of daily activities with physical imitation of the same actions with the paretic limb. Moreover, fMRI showed a significant increase in the bilateral ventral premotor cortex activity of patients treated with AO compared to the control group, which only watched geometrical images (Ertelt et al., 2007). Similar functional outcome of the upper limb confirmed its positive effect over years (Franceschini et al., 2010; Sale et al., 2014; Zhang et al., 2019). Furthermore, AO training show improvement also in scales that evaluate the independence in daily activities (Franceschini et al., 2012; Fu et al., 2017) and in kinematics features (Kim & Kim, 2015).

Despite the limitation of these studies deriving from the protocols that not permit to establish precisely the reason of improvement, it must be kept in mind that scientific literature has provided controversial results on the effect of AOT in stroke patient with an impaired limb, thus appear difficult draw firm conclusion of its efficacy.

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CHAPTER 3

NEUROPLASTICITY, COGNITIVE RESERVE, BRAIN RESERVE

3.1 Neuroplasticity

Neuroplasticity refers to the ability of the nervous system to change its activity in response to intrinsic or extrinsic stimuli by reorganizing its structure, functions, or connections. From a clinical point of view, it is the process of brain changes after damage, such as a stroke or traumatic brain injury. These changes can either be beneficial (i.e., restoration of function after injury), neutral (i.e., no change), or detrimental (i.e., can have pathological consequences) (Puderbaugh & Emmady, 2021).
Neuroplasticity is manifested through two major mechanisms:

2. Neuronal regeneration/collateral sprouting such as synaptic plasticity and neurogenesis.
3. Functional reorganization such as equipotentiality, vicariation, and diaschisis.

Neuroplasticity is fundamental for the neurological recovery and restoration of function in the paretic limb in accordance with the residual capacity. It manifests through several mechanisms such as: *sprouting* that is the regeneration of the axon and correlated myelin after peripheral nerve injury and the emergence of axonal collaterals of surrounding surviving axons to re-innervate denervated postsynaptic regions; *synaptogenesis* that is the increase in synaptic endings on neurons spared from damage but deprived of part of their afferences; *synaptic receptor rewiring* that occurs in surviving neurons by increasing their NDMA-type glutamate receptors; s*ynaptic de-inhibition* represents a transient cortical depression of function affecting neuronal areas far from the site of injury but functionally linked to it; through *brain reorganisation*, when damaged areas are offset by others that were not previously involved in that specific function. Phenomena of neuroplasticity described above occur in the first 3 months after damage and determinate the intrinsic recovery. After that, function is not recovered but only compensated for by residual structures that remain intact, thanks to behavioural modifications. In this way, recovery continues slowly with the so called adaptive or extrinsic recovery and corresponds to functional replacement (Draganski et al., 2008).

The combination of results achieved by basic neuroscience, based on *in vivo* models, and rehabilitation practice has made it possible to postulate 10 experience-dependent plasticity principles (Warraich & Kleim, 2010):

1. *Use it or lose it*; if a failure of driving specific brain functions occurs, this can lead to functional degeneration;
2. *Use it and improve it*; Training which drives a specific brain function can lead to improving abilities.
3. *Specificity*, the nature of the training experience establishes the nature of the change in the brain (so called plasticity).
4. *Repetition matters*; plasticity requires enough repetition.
5. *Intensity matters*; plasticity requires intensive training.
6. *Time matters*; different forms plasticity in the brain occur at different times during training.
7. *Salience matters*; the training experience have to be meaningful to the subject to cause plasticity
8. *Age matters*; training-induced plasticity happens more readily in younger brains.
9. *Transference*; change in function as a result of one training experience can even lead to learning other analogous skills.
10. *Interference*; plasticity that result in bad habits can interfere with learning good habits.

These principles should be adopted in clinical rehabilitation in order to improve functional recovery, activities and quality of life of patients although it is necessary to better understand how training experiences interact with neural reactions to the brain damage, compensatory behavioural changes, and age, as well as how to combine rehabilitative training with other treatment approaches. Moreover, it is key to understand time windows in which training can be optimally and safely applied.

3.1.1 Neuroplasticity in Stroke and Multiple Sclerosis

Regarding stroke patients, pharmacological, biological and electrophysiological approaches are being developed to improve neuroplasticity-induced and training-induced functional gains. The intervention on nervous system includes electrical stimulation to peripheral nerves and muscles in order to assist stroke patients with hemiparesis move their affected limbs. Moreover, PNS stimulation can influence the CNS via afferent pathways, and some PNS stimulation protocols have been designed specifically to induce cortical plasticity. Stimulation of the CNS, specifically the primary motor cortex (M1), may enhance motor rehabilitation after stroke. TMS and direct current stimulation offer non-invasive strategy in order to stimulate cortical surface of the brain. At the same time, epidural electrodes could be surgically implanted to stimulate the motor cortex directly. Since limb movement is accompanied by a transitory raise in excitability in the corticospinal tract, a lot of researchers have investigated the adoption of electrical stimulation—either applied transcranially or through implanted epidural electrodes to exogenously amplify the excitability of the stroke affected ipsilesional M1 to increase function. Most studies of ipsilesional M1 stimulation have shown an improvement in at least one motor ability or improved performance on precise functional rehabilitation tests. Interventions that stimulate the M1 are still at the experimental stage. Moreover, the efficacy of these strategies depend on the intensity, lasting and frequency of the electrical stimulation, as well as on the area of the brain being stimulated. Metabolic brain imaging not infrequently shows abnormally high levels of activity in the contralateral motor cortex of patients with stroke. Although functional role of this activity is unknown, electrophysiological data indicate that interhemispheric inhibition of the ipsilesional M1 by the contralesional M1 is abnormally persistent during movement of the paretic hand. Together, these data support the hypothesis that interhemispheric competition might be a factor that influences motor rehabilitation after stroke. Therefore, the contralesional M1 has become a major target for interventional therapy for poststroke rehabilitation. Many studies have demonstrated significant improvements in both simple and more complex tests of hand function in subjects with subacute or chronic stroke who have undergone stimulation to decrease excitability in the contralesional M1 although, recently, a trial has shown contradictory results (Dimyan & Cohen, 2011).

Histopathological and functional magnetic resonance imaging (fMRI) investigations have provided interesting evidence for neuronal plasticity in MS patients. Increased neuronal expression of growth-associated proteins was found in MS and its model compared with traumatic cases. Furthermore, altered cortical activation patterns on fMRI were shown to be linked with clinical rehabilitation and a more favourable disease course. Some researchers assume that training programs may improve neuronal plasticity (on fMRI) and enhance short-term motor and cognitive performance in MS subjects. At the same time, transcranial magnetic stimulation improves functional connectivity, which could be important for cognitive rehabilitation, and that some pharmacotherapy can enhance memory in MS patients with baseline memory damages. However, to date, it is not clear if the positive effects can be sustained long term. Moreover, the diffuse disease process in MS excludes use of aimed interventions and, for pharmacotherapy in particular, there is hazard of inducing maladaptive plasticity. Although the modulation of brain plasticity is an fascinating approach to promote functional recovery, relevant challenges still need to be addressed before such strategies can be translated adequately to clinical practice (Kerschensteiner, 2017).

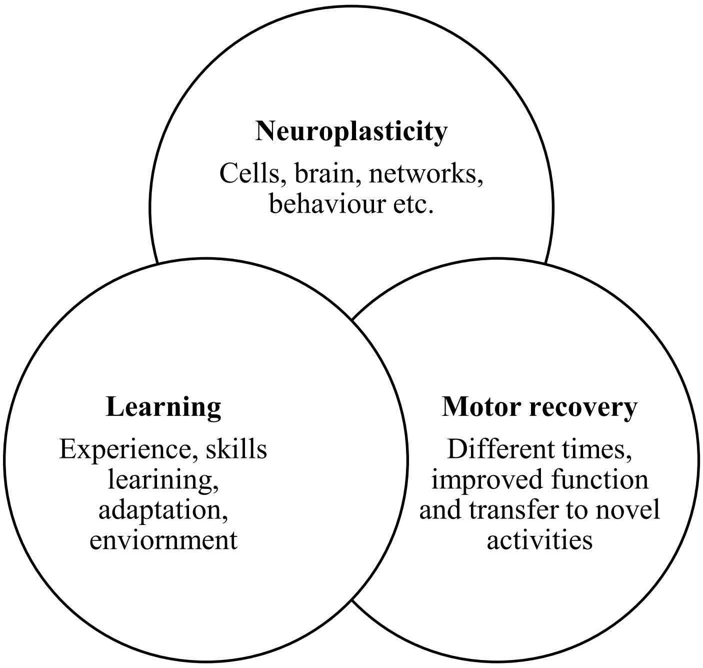

Figure 1. Concept map depicting the three main concepts and the potential associations between them

3.2 Reserve

The concept of reserve has been a major research goal on protective factors involved in containing the outcomes of neurological damage and disease. Reserve has been proposed as a mechanism by which to explain variability in functional outcomes following neurological insult (Stern 2002, 2003, 2009). A great deal of knowledge on the argument of reserve derives from research in Alzheimer's disease. Katzman and colleagues (1988) identified a subgroup of Alzheimer's patients who, despite having high levels of pathology and neurodegeneration, were found to exhibit fewer functional deficits than their age and pathology-matched counterparts. Theorists have developed two empirically supported models of reserve, frequently defined as active and passive reserve (Sole-Padulles et al., 2009; Stern, 2009; Satz, 1993). Active reserve represents the set of mechanisms that contribute to increased flexibility and efficiency of neural resources which enable a subject to actively compensate for neurological injury (Stern, 2009). The passive model of reserve incorporates the theory to that once neurological injury or disease surpasses an individual's capacity threshold, only then will the individual exhibit symptoms of brain damage (Sole-Padulles et al., 2009; Graves et al., 1996; Satz, 1993). Each subject has a pre-set, quantifiable capacity (e.g., brain size, number of neurons; Katzman, 1993; Mortimer et al., 1981) that determines the amount of damage can be sustained before functioning is compromised. Generally, the active and passive models are used in the context of cognitive and brain reserve, respectively. Both models hypothesize subjects with higher reserve (e.g., larger brain volume, greater cognitive resources) will exhibit fewer functional deficits compared to injury-matched counterparts with lower levels of reserve.

3.2.1 Brain Reserve

Through the concept of brain reserve (BR), researchers explain subjective differences in the manifestation of functional deficits due to brain pathology based on an individual's physiological capacity or threshold (Satz, 1993). This passive model of reserve justifies that larger brain size accounts for inter-individual variability in neurological functioning post-insult due to a greater capacity to withstand damage. Through the measurement of brain volume, head circumference as an indirect measure of brain volume and the neuronal count, it is possible to evaluate the BC (Bigler et al., 1999). Since enriching environments, measured as proxies of cognitive reserve, can contribute to increased synaptic density and neuronal growth improving brain reserve, it could be assumed that BR and CR are not independent constructs (Brown et al., 2003; Nilsson et al., 1999). Although apparently overlapping, researchers suppose these constructs do contribute differentially to outcomes of neuropathology, as correlations among the constructs are not so marked as to suggest the two are one in the same (Wickett et al., 1994). Seeing as CR and BR account for significant variability in outcome of neurological injury/disease, they are important factors to consider in the context of understanding variety of outcomes in stroke and multiple sclerosis.

3.2.2 Cognitive Reserve

According to supporters of the theory of CR, individuals can rely on unconventional or more efficient brain networks to balance for increased demand on the damaged brain, rather than sole reliance on static physiological functions (Stern, 2003). Therefore, CR is not an inert characteristic. It represents a mutable factor that can be modified throughout the lifespan (Bigler & Stern, 2015; Richards & Sacker, 2003). There are many factors that impact on CR: genetics, intellect, type of occupation, education level, abundance and quality of social networks, and avocation (Bennett et al., 2006; Stern, 2003; Richards & Sacker, 2003; Scarmeas et al., 2001; Alexander et al., 1997; Stern et al., 1994; Stern et al., 1992). It is assumed that mentioned factors represent opportunities for improving neural resources laying the foundation for greater compensation or flexibility to optimise function in the context of brain injury. In the context of neural compensation, brain damage has been investigated through the employment of functional magnetic resonance imaging (fMRI) methodologies. Interestingly, fMRI allows to detect the recruitment of alternative brain regions, not otherwise usually activated in non-brain injured subjects, during cognitive task engagement (Ji et al., 2018; Steffner et al., 2011; Bartres-Faz et al., 2009). It is important to highlight that while evidence supports neural compensation as a potential mechanism of CR, researchers note that compensation does not undoubtedly indicate optimal functioning. Indeed, a greater compensation could be accompanied by a weaker behavioural performance (Stern, 2009; Grady et al., 1994). Therefore, researchers have also investigated another potential mechanism of cognitive reserve. It has been shown that neural efficiency provides support for greater flexibility and capacity of existing neural networks allowing preservation of cognitive function (Zarahn et al., 2007). Since, the adoption of neuroimaging techniques is expensive, researchers have often relied on measures of intelligence quotient (IQ), education, or occupational attainment as affordable and steady instruments to evaluate the quality of CR (Stern, 2003; Alexander et al., 1997; Stern et al., 1992). Such proxies are thought to be representative of genetic and environmental factors that link to the enhancement of neuronal resources. An instrument for a standardized measure of the cognitive reserve accumulated by individuals throughout their lifespan is the Cognitive Reserve Index questionnaire (CRIq); it is includes demographic data and items grouped into three sections: education, working activity and leisure time, each of which returns a subscore (Nucci et al., 2012).

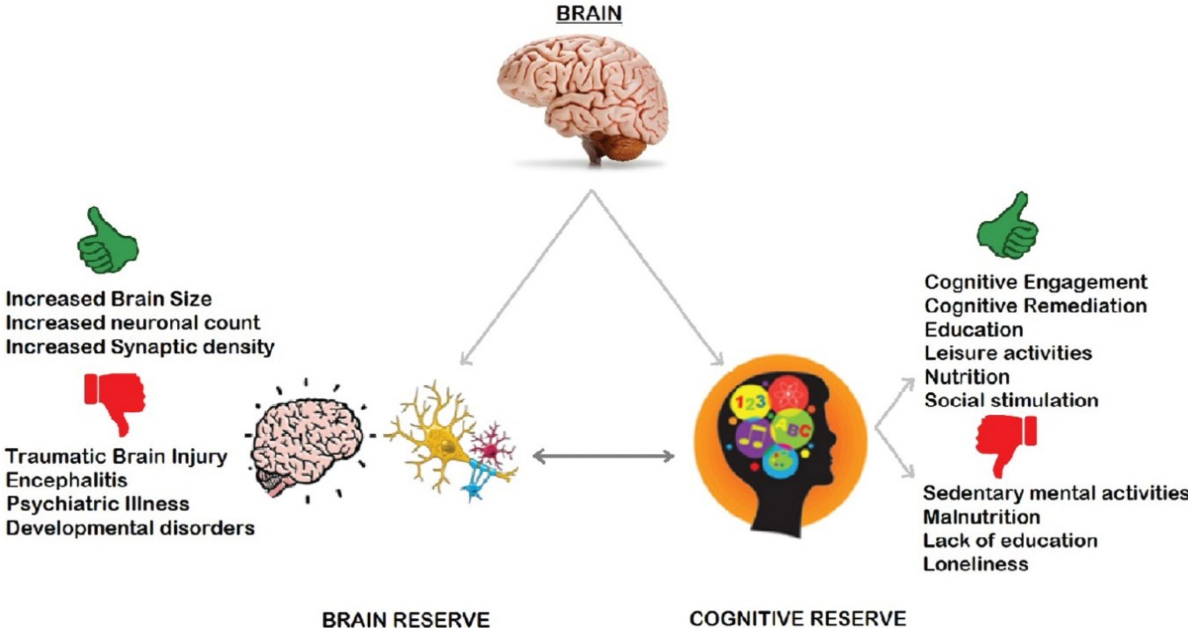

Figure 2. Dynamic triad of cognition (Pinto & Tandel, 2016)

3.2.2.1 Cognitive Reserve Theory

Originally, CR theory was proposed to elucidate the differences between clinical symptoms and severity of AD upon autopsy. This theory postulates that the practise of mental and physical activities might protect the brain against cognitive decline despite of the physiological cognitive decline and any damage induced to the brain. Improving of the CR occurs when neural processing underlying cognitive performance becomes more effective and efficient. Interesting, it is assumed that subjects can continue to build their CR throughout life. High CR is associated to a better ability to take on brain pathologies without the onset of cognitive symptoms. Therefore, CR represents a protective factor link to compensatory brain mechanisms able to counteract brain damage. On the other hand, brain reserve refers to subjective differences in brain structures that make us more resilient to neurodegenerative and psychiatric diseases (Stern, 2002).

3.2.2.2 The role of cognitive reserve in Stroke

Mechanisms of stroke recovery, intended as cognitive/motor/psychological changes that occur poststroke likely driven by "compensatory" mechanisms, are likely influenced by cognitive reserve. Individual differences in neural compensatory mechanisms (e.g recruitment, retraining) of unaffected brain region to maintain performance, might partially constitute differences in cognitive reserve, as neural compensatory mechanisms parallel the mechanisms advanced by cognitive reserve theory (Stern, 2002, 2009). However, the mechanism through which cognitive reserve develops, and promotes neuroprotection, remains to be investigated (Stern et al., 2018). Among the various hypotheses about the cognitive and neural mechanism of cognitive reserve there are: more flexible cognitive processing, increased synaptogenesis, and neurogenesis) and the upregulation and expression of brain-derived neurotropic factor, known to facilitate neuroplasticity (Buchman et al., 2016; Nithianantharajah & Hannan, 2009). According with the original hypotheses of cognitive reserve theory, in stroke survivors, it was used cognition as a primary outcome for the majority of evidence for cognitive reserve. Through two longitudinal studies it was demonstrated that cognitive reserve (defined as years of education) maintain global cognition and memory, reduces the development of aphasia and dementia following stroke, independently of socioeconomic status (Booth et al., 2013; Ojala-Oksala et al., 2012). In addition, a significant reductions in the severity of language impairment following stroke was associated with cognitive reserve (operationalized as educational attainment), independently of age, sex, stroke volume, and socioeconomic status (González-Fernández et al., 2011). Other evidence indicates that individuals with higher educational level, thus with higher cognitive reserve, are at a reduced risk of developing dementia subsequent transient ischemic attack and stroke (Mirza et al., 2016; Malsch et al., 2018). Analogously, a cross-sectional study confirmed that those with higher cognitive reserve (defined as years of education) had less cognitive deficits and functional disability (measured with modified Rankin Score) in the acute setting poststroke (Umarova et al., 2019). Another studies showed that stroke survivors with higher cognitive reserve (measured as educational or occupational attainment) exhibited significantly upper probability of experiencing reduced disability, fatigue, functional burden in ADL and depression following stroke (Grube et al., 2012; Bettger et al., 2014; Marsh et al., 2018). Physical activity (i.e. aerobic exercise and strength training), has been shown to rise brain volume and preserve cognition in people with stroke (Colcombe et al., 2006; Marzolini et al., 2013). Moreover, higher cognitive reserve (measured as years of education) has been related with reduced long-term mortality, even after adjustment for stroke severity, white-matter lesions and demographil charcteristics (i.e. age, sex, marital status) (Ojala-Oksala et al., 2012). An autopsy study evaluated a gamma of neuropathological indices founding that very low level of education (between 3 and 4 years) modify the relationship between lacunar infarcts and cognitive ability prior to death, independently of socioeconomic status and other comorbidities (Farfel et al., 2013). Besides the years of education, also premorbid intelligence was reported to be a stronger predictor of cognition following stroke; to date these considered the most robust indicators of cognitive reserve (Makin et al., 2018; Rosenich et al., 2019).

The influence of cognitive reserve on mood is not most clear; but it should be recognized that post stroke deficits, such as cognitive impairment, often reflect badly mood (i.e. depression) and are probable interrelated (Babulal et al., 2015; Backhouse et al., 2018). It was studied also whether social integration modify the course of poststroke cognitive recovery; the result show that baseline social ties and emotional support alone predicted cognition at 6 months poststroke and greater cognitive improvement. Thus, social ties might be an indicator of cognitive reserve (Glymour et al., 2008).

Hence, variuos studies support that cognitive reserve influences cognitive rehabilitation outcomes after stroke (Umarova, 2017; Umarova et al., 2019) but its impact on motor rehabilitation outcomes has so far not been evaluated. A study involving patients with Parkinson's disease, demonstrated that patients with lower cognitive reserve benefit more from a conventional rehabilitation than those with higher cognitive reserve (Piccinini et al., 2017). Maybe, the reason derive that conventional rehabilitation may not be sufficiently stimulating for individuals who performed a job needing great cognitive engagement or who obtained a high level of education. In line with the aforementioned study, another unpublished research on Parkinson's disease patients showed that who have with higher cognitive reserve have better motor outcome from virtual reality than those with lower cognitive reserve. Padua and colleagues (2020) evaluated whether cognitive reserve influences the motor outcome in patients following stroke treated with robotic or conventional therapy and if it may impact one treatment rather than another. Considering all sample, it was found a weak correlation between the cognitive reserve index (as leisure time) and motor ability evolution. Among the patients who performed a robotic rehabilitation, a moderate correlation emerged between the cognitive reserve index (as working activities) and motor performance evolution (Padua et al., 2020). Combining these results, it could hypothesized that patients with a higher cognitive reserve, might have more experience with technology and benefit more from technological rehabilitation, contrary to patients with lower cognitive reserve that might benefit more from conventional therapies. In general, information about the cognitive reserve are useful in customizing the intervention.

Rosenich et al., (2020) in a review have expose the potential of cognitive reserve in stroke, referencing to the reduced burden of stroke survivors disability, health promotion, treatment and secondary prevention of cognitive impairment. About this, authors encourage stroke clinicians and researchers to better account the role of premorbid, lifestyle-related variables. An evaluation of cognitive reserve preceding to discharge would give important information about individual patient features and previous capacities and help define and optimise rehabilitation treatment (Fortune et al., 2016).

3.2.2.3 The role of cognitive reserve in Multiple Sclerosis

The brain reserve hypothesis affirm that larger maximal lifetime brain volume (MLBV), estimated with intracranial volume or head size, preserve on cognitive decline (Satz, 1993). That is, cognitive impairment emerges when brain volume falls beneath a critical threshold; individuals with larger MLBV support greater illness burden earlier reaching this threshold. Indeed, elderly individuals with larger MLBV have better cognition (Farias et al., 2012) and inferior risk of dementia (Graves et al., 2001). Starting from this premise, Sumowski et al. (2013) investigate if MLBV (brain reserve) defends patients with MS from disease-related cognitive impairment. Then, they studied if cognitive reserve gained through life experience (i.e. leisure activities) protects against cognitive decline independently of MLBV. Cognitive status was positively associated with intracranial volume, revealed that larger intracranial volume attenuated the impact of disease burden on cognition. Moreover, a higher-level education and more leisure time activities, predict better cognition. They provide evidence that lifestyle choices safeguard against cognitive impairment independently of genetic factors outside of one's control.

Thus, the protective role of cognitive reserve after brain damage has been reported also for multiple sclerosis (Fuchs et al., 2019). For example, it was showing that lifetime intellectual enrichment attenuates the effect of disease burden on cognition (Sumowski et al., 2009; Sumowski et al., 2010a; 2010b; 2010c). In a recent cross-sectional study of MS patients, age and cognitive reserve were the only significant predictors of cognitive impairment (Amato et al., 2019). Cognitive reserve has been confirmed as the strongest predictor of cognitive impairment, after adjusting for different confounder factors (Benedict et al., 2010; Nunnari et al., 2016). In a recent meta-analysis, the weighted effect sizes between cognitive reserve and various cognitive domains were found to be significant and moderate (Santangelo et al., 2019). Artemiadis et al. (2020) evaluated the role and the impact of cognitive reserve (measured with CRIq) on cognitive performance (i.e. information processing speed, verbal and visuospatial memory); 38.4% of 526 MS outpatients be failure in cognitive tests, thus presented a cognitive impairment and the CRIq score of cognitive impairment patients was lower. The link between cognitive performance and cognitive reserve, using the CRIq, has been

validate by previous research in MS (Chillemi et al., 2015; Nunnari et al., 2016) but also in other neurological diseases as well in healthy subjects (Santangelo et al., 2019; Stern, 2002). Artemiadis et al. (2020) revealed that 12.2–23.7% of cognitive performance in MS was explained by CRIq, disability and depressive symptoms. Specifically, it was found a significant interaction between CRIq and disability (measured by EDSS) for information processing speed; this suggesting that with increment disability, information processing speed performance decreases more in patients with low rather than high cognitive reserve. The moderating role of cognitive reserve has been documented with respect to the effect of lesions or brain atrophy on cognitive performance (Santangelo et al., 2018). Regarding depressive symptomatology, they displayed that patients with low rather than high CRIq score show more depressive symptoms. About this mood alteration, the patients may tend to underreport positive events such as social activities or leisure (Dalgleish & Werner-Seidler, 2014).
In conclusion, even in multiple sclerosis, the importance of identifying the cognitive reserve index as a potential predictor of outcome is highlighted. The role of the reserve in optimizing the efficacy of certain conventional and non-conventional treatments for MS remains to be explored.

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CHAPTER 4

ENGAGEMENT

4.1 The definition of “engagement”

Nowadays, there does not seem to be an all-encompassing definition of engagement shared by all. Bright et al. (2015) suggested a theoretically and empirically derived description of engagement: “Engagement is a co-constructed process and state. It incorporates a process of gradually connecting with each other and/or a therapeutic program, which enables the individual to become an active, committed and invested collaborator in healthcare”. In their conceptual review highlights that engagement is multi-faceted and co-constructed. Engagement was conceived in two interconnected ways, as a process ("engaging with") and a state ("engaged in"). The process of engagement focus on creating a connexion between the patient and practitioner/service. The state of engagement is an internal state expired by the patient and explicated through observable behaviours. Thus, engagement includes a relational process and the failure to engage is not only a patient responsibility. An interesting review finding was that the patient perceptions of the practioner’s engagement may be fundamental in their decision to engage; hence engagement is co-constructed; i.e. that the healthcare provider plays a meaningful role in patient engagement. Moreover, the review underline that the status of engagement encloses a dynamic internal state expressed across observable behaviours and consider engagement as being on a continuum. Relating to the last point, the provider should be identify where the patient is on the continuum and what may influence, or what is influencing their movement along the continuum. There is still not a universally recognized concept of "full" engagement intended as desire endpoint, that potentially correspond in incorporating collaboration, contribution, active participation and emotional investment. However, in rehabilitation contest, is not be always possible contributing to decision-making due to the presence of mood, cognitive or social communication deficits (Bright et al., 2015). It follows that the practioner should be more reflective approach wondering how can facilitate engagement in their patient.

4.2 Factors that influence engagement

An important point in engagement study is the client-centred perspective. Defining patient rehabilitation in a holistic perspective, intentionally focused on the individual, promotes client-centred and is based on its strengths; so, may help rehabilitation be more individualized and promote engagement in rehabilitation (MacLeod & McPherson, 2007; Gzil et al., 2007; Wilding & Whiteford, 2009). To operationalize a client-centred approach to rehabilitation is advisable beginning by getting to know the person and their story, and identifying yours needs. In conclusion, focus shift from “what can I do for this person” to “who is this person and what do they need”. Lequerica et al. (2009), using a survey approach, examined the impressions of physical and occupational therapist on therapeutic engagement among their patients. In general, there were identified as points influencing patient engagement and participation in rehabilitation therapies both intra-personal factors (emotional status, attitudes, or beliefs) and inter-personal factors (type of treatment, clinician's behaviour, involvement of family members). Research has shown that depressed mood, cognitive impairment, and fear of pain, as well as, the number of comorbidity and side effects of medications, are the most frequently encountered barriers impacting patient engagement. Also, an overprotective family member is often seen as a obstacle to independence. While, the most commonly reported practise for enhancing therapeutic engagement, is that of making treatment' tasks meaningful and related to the patient personal goals. To facilitate motivation, a good seems be practice treating the patient as an active participant in their recovery that is including it in goal setting. In addition, the rapport with therapist is important and correlate with patient's motivation. To increase patient engagement, the therapist in treatment setting should be providing the patient with control, instruction, empathy and support. In the motivational model developed by Atkinson (1964), the motivation is affected by patient's perceptions of the likelihood and value of a successful outcome and the costs of the rehabilitation course. Bright et al. (2017) through a qualitative study of stroke patients, explored how the practioner's engagement and disengagement occur, and how these may influence patient care and engagement. They concluded with some clinical messages. First, practitioner and patient engagement in rehabilitation is affected by their perceptions of the other's engagement. Practitioner engagement is determined also by their knowledge and confidence. Secondly, practitioner engagement/disengagement can impact on how the patient experiences rehabilitation, seems to influence patient care and clinical decision making.

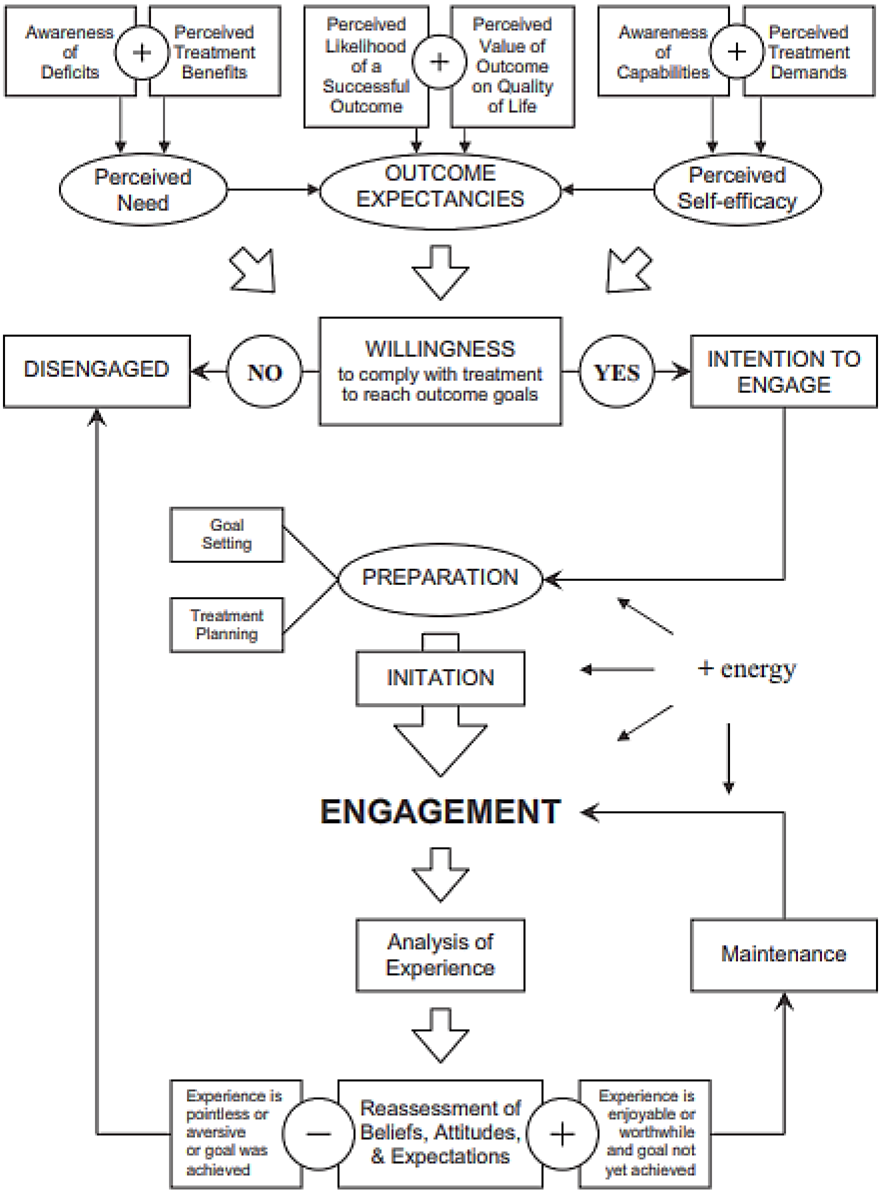

Figure 9. Model for therapeutic engagement in rehabilitation (Lequerica & Kortte, 2010)

4.3 The role of engagement in rehabilitation

The patient engagement is consider a key concept in rehabilitation and in general in healthcare context (Horton et al., 2011). It was demonstrated that the rehabilitation benefits are restricted if the patient is not completely engaged in the process (Kortte et al., 2007; Medley & Powell, 2010). The degree of engagement has been correlated with improved functional gain during inpatient rehabilitation and levels of functioning after discharge, as well as with higher levels of adherence and attendance and lower levels of depression (Lequerica et al., 2006; Kortte et al., 2007). Lack of patient engagement within rehabilitation can hinder the functional recovery of cognitive and motor functioning and increase patient's time in hospital (Lequerica et al., 2009, Lequerica & Kortte, 2010). By the factor analytic research performed by Matthews et al. (2002), engagement is considered on a continuum distinguishing high engagement (interest and enthusiasm) with low engagement (indifference and apathy), where higher levels of engagement should be related with better involvement and participation in rehabilitation. Consequently, level of engagement, is conceptualized as a quality that depicts 'how' one is participating. It is therefore evident its importance in rehabilitation outcomes, if it considered that poor participation in physical/occupational therapies are linked with less functional improvement and with major length of stay (Lenze et al., 2004). Relative to physical therapy participation, it was suggested that the emotional status, like anxiety and fear of pain, limit the full engagement (Lejbjuk, 2006). Moreover, depressed mood and negative attitude toward treatment can lead to decreased motivation, which is a central factor in patient engagement and participation (Lee & Kim, 2003; Lenze et al., 2004). One review reported five categories of factors influencing engagement: illness-related (symptoms, treatment course, patient's experience, severity of illness); patient-related (i.e. patients' knowledge, demographic characteristics, emotions and coping style); practioner-related healthcare (knowledge and beliefs and specific role); setting-related healthcare (primary or secondary care); and task-related (medical knowledge required and whether the required patient behaviour challenges clinicians' clinical abilities) (Davis et al., 2007).

4.4 Engagement and digital technologies

Patient engagement is defined a key element in neurorehabilitation in order to promote greater neuroplasticity changes and functional outcomes (Danzl et al., 2012). The use of digital technologies in neurorehabilitation field has prompted the possibility to direct the rehabilitation at patients' homes (Agostini et al., 2015, Perry et al., 2011). In fact, there were been considered as a helpful resource for improving patients' participation and have an active role in patients' health-care process (Maye & Cox, 2017; O'Neil et al., 2018). Digital technologies in rehabilitation has the goal of providing information and support emotional, behavioural, and physiological traits of the pathology within a stimulating and enriched environment. Recently, a systematic review of the role of engagement in telerehabilitation in patient with neurological disease was carried out. Results displayed a growing interest in making new telerehabilitation protocols in neurorehabilitation for get better patients' engagement by promoting self-awareness and self-management of patients, patients' motivation, and emotional support. These subcomponents of engagement have been described as the emotional, behavioral and cognitive dimension of patient engagement (Matamala-Gomez et al., 2020).

The use of telerehabilitation systems can enhance the patient engagement by conducting their rehabilitation training at home. One of the rehabilitation instruments in multiple sclerosis and stroke are virtual environments and serious games. Frome (2007) proposed a model that identify the four factors that induce positive emotions by using these games: a narrative factor (feel the emotions of the virtual figure); game-playing factor (sensation of satisfaction when winning the game, or as opposite, frustration); the simulation factor (the game must provide engaging activities); and the aesthetics factor (artistic aspects of the game). All these factors can favour engagement of the patient by employing various technological sources at their own home, like virtual reality systems (Turolla et al., 2013), videogames (Argenton et al., 2014), mobile e-health (Tachakra et al., 2003), and e-learning platforms (Sinclair et al., 2015).

4.5 Engagement in Multiple Sclerosis and Stroke

MacDonald et al. (2013), proposed a review with the aim was gain a more in-depth comprehension of the barriers and facilitators to engagement in rehabilitation following stroke. It was identified seven principal points from included papers, describe below. Goal setting maybe affect the way the patient engages in their rehabilitation and was considered most efficacious when patients were actively involved in the goal setting process and when these were based on negotiation and interaction. Patients were most engaged when the rehabilitation intervention and environments were personalised to the patient. Factors identified to influence patient engagement were the approach of practioner, the level of support they provided and their perceived level of involvement in the rehabilitation process. The level of familiarity and perceived importance of rehabilitation was suggested as key element in the level of rehabilitation's engagement; indeed, if patients perceived their rehabilitation to be non-meaningful and non-functional, they appeared more probable to disengage. Furthermore, it was discovered that the autonomy level of patient can have a direct consequence on the degree that they actively engagement, with raised autonomy resulting in greater motivation. Patient centred rehabilitation, that is, structured around the interests, goals, and choices of the patient, was seen to empower and foster patients to be more active role in their rehabilitation. Moreover, emerged that educating patients survivors about their pathology and discuss for rehabilitation choices, promote them to take on a more central role in rehabilitation course. Lastly, providing feedback was seen to probably influence patient engagement in specific rehabilitation interventions, supplying patients with positive strengthening and improving motivation.

Patient engagement is particularly important also in chronic illness, as Multiple Sclerosis, which necessitates lifelong therapy (Rieckmann et al., 2015). A cross-sectional survey of about 200 MS patients identified that MS-related QoL and MS-related self-efficacy correlated significantly with patient activation (Goodworth et al., 2016).
The MS in the 21st Century Steering Group delineated a group of themes that demand action with concern to MS patient engagement. Rieckmann et al., (2015) discuss these points by their perspective and identify the barriers in patient engagement and strategies for overcoming them. These are named below.

- Setting and facilitating engagement by education and confidence-building. A necessary condition to make sure that a patient become engaged is the establishment of an effective and mutually respectful patient–physician relationship; indeed, patients affirm that good communication with their doctors increases their confidence with the healthcare course (Duffy et al., 2004; von Puckler, 2013).
- Increasing the importance placed on QoL and patient concerns through patient-reported outcomes. Patient-reported outcomes incorporate information that reflects health and well-being from patient's perspective, comprising how the illness and medical/rehabilitation interventions affects their QoL.
- Providing credible sources of accurate information. Taking into consideration the intricacy of MS disease and the complexity of the management options disposable, is fundamental to an MS patient to receive reliable, accurate and relevant information (von Puckler, 2013).
- Encouraging treatment adherence through engagement. With the availability of therapies for MS, problems with adherence to these complex therapy regimens under chronic conditions have been noted (Klauer & Zettl, 2008). The origin of non-adherence include forgetting medication, MS-related disability affecting capability to medicate, patient disagreement with necessity for care, costs and poor social sustain. Sometimes, treatment adherence reflects also the dynamics of the physician–patient relationship (Martin et al., 2005; Cerghet et al., 2010; Saunders et al., 2010; Lugaresi et al., 2012). In order to improve adherence to therapy in MS, methods as telephone advice or motivational interviewing could be efficacious.
- Empowering through a sense of responsibility. The responsibility to engage the patient in their health reclines with everyone involved with their care (as health-related practitioner and caregiver), as well as with the patient itself.

In a narrative review is reported that working in a multidisciplinary way is necessary in rehabilitation not only because of continuity and optimized outcomes but also to ameliorate engagement of MS patient. Because engagement of the person with MS is multifactorial, every practioner may center on one or more of these factors and in this mode affecting engagement (Peeters et al., 2020). Results of a systematic review display that multidisciplinary treatment improves self-care, mobility, activities and participation short-term and diminish disability (Amatya et al., 2017). Over the therapeutic course, it is prominent to raise information of MS patient functioning from a holistic perspective. All type of information can be used to program or adapt the therapeutic process with personalized goals. This may gain the intrinsic motivation to continue treatment, and thus improve therapy compliance. In self-management interventions, the focus of attention is on the ability to self-steer decisions and actions, modify behaviours, and keep emotional stability (Khan & Amatya, 2017; Salomè et al., 2019). In addition, cognitive decline present in MS may play a role in compromised engagement. In this regard, Hynes and Forwell (2019) portray the development of a cognitive occupation-based program for MS patients to give a holistic programme to ameliorate participation in activities of daily life compromised by cognitive deficits. Finally, Kayes et al. (2011) carried out a qualitative study to detect the facilitators and barriers to engaging in physical activities in MS and identified some contradictory convictions in these patients. These are: the cycle of activity and inactivity; a thin line among beneficial and harmful exercise; the physical activity as a lose of time since of the unclear advantages and as action to worsening of symptoms; finally, physical activity as a possibility to maintain abilities.

In conclusion, still few studies to date have investigate the key factors that can affect engagement from the patients' perspective. A profound comprehension of engagement within different neurological illness may help providers to improve their clinical skills and adapt these to the single patient's needs, to best facilitate engagement and enhance the effectiveness of rehabilitation interventions. The same importance covers the study of the practioner's engagement from the patient's perspective; the patient opinion may be seen as a prompt to critically reflect on what the clinician is doing and how the two parties are working jointly. Thus, the importance of sharing clinical experience is emphasized to be useful to other rehabilitation professionals in the treatment of patients who are difficult to involve in the rehabilitation process.

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CHAPTER 5

TELEMEDICINE AND COVID-19

5.1 Definition of telemedicine

Telemedicine is a method of providing health care services, using innovative technologies, in particular Information and Communication Technologies (ICT), in situations in which the health professional and the patient (or two professionals) do not are located in the same area. Telemedicine includes the secure transmission of medical information and data in the form of texts, sounds, images or other forms necessary for the prevention, diagnosis, treatment and subsequent monitoring of patients. However, digital mode health service does not replace traditional health care in the personal doctor-patient relationship, but integrates it to potentially improve effectiveness, efficiency, and appropriateness. Telemedicine must also comply with all the rights and obligations of any health act.

Telemedicine services can be classified into the following macro-categories:

- Specialist tele-medicine: concerns the health services that can be provided remotely within a specific medical discipline. Telerehabilitation is a branch of telemedicine, defined as the use of communication and information technologies to provide remote clinical rehabilitation services. It is therefore clear how there can be a union between telerehabilitation and the COVID-19 emergency.
- Telehealth: concerns the systems and services that connect patients (especially chronic ones) with doctors to assist them in the diagnosis, monitoring, management and empowerment.
- Teleassistance: concerns a social assistance system for taking charge of the elderly or frail person at home, through the management of alarms, activation of emergency services, "support" calls from a service specialized centre.

The modalities in which telemedicine can be provided are in real time, deferred or in mixed mode. The real-time mode can use applications that allow the audio-video combination, while the delayed mode uses apps that can be created specifically for this purpose; however, they do not allow a real-time exchange between healthcare professional and patient (Kairy et al., 2009; Ministry of Health, 2014).

5.2 Telemedicine during COVID-19

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic has led to an expansion of the use of telemedicine. Suddenly and unexpectedly, hospitals had to suspend or reduce non-essential services in order to reduce the spread of the virus; telemedicine has thus become an alternative for providing assistance to patients, while maintaining social distancing and limiting contagion. During the emergency, even the physiatrist, which normally would not have made use of telehealth, was forced to turn in this direction (Tenforde et al., 2020). Despite this, physicians' familiarity with telemedicine and the literature description of best practice remain limited.

In the emergency context, the World Health Organization (WHO) has released a document containing considerations on disability during the pandemic and states that COVID-19 may have a stronger impact on the disabled. Among the recommendations that the WHO addresses to health professionals, there is that of activating remote care programs through telephone consultations, messages, and video conferences: these programs are not only related to the needs deriving from a possible COVID-19 infection, but also aimed at covering the rehabilitation needs of disabled people and protecting their health status (WHO, 2020).

The relationship between disability and the pandemic must necessarily be considered: the difficulties inherent in the disability itself and the constraints caused by the pandemic can cause a double suffering in the patient. Lebrasseur et al. (2020) conducted a rapid review of the published literature to assemble results from studies about the impact of the COVID-19 pandemic on people with physical disabilities. Several impacts on daily functioning such as a decrease in access to healthcare have been noted during the pandemic, as changes in social and lifestyle habits, mood changes and decreased levels of physical activity. Moreover, people with physical disabilities might be particularly likely to be negatively affected in psychosocial area, but evidence is poor. It was noted that those with a disability experienced greater increase in anxiety and depression than people without a disability, over a poorer quality of life and sleep, less psychological wellbeing and lower levels of social contact (Steptoe & Di Gessa, 2021). About this, during the lockdown period, there was a need to provide adequate rehabilitation programs to people in quarantine or with reduced mobility in order to reduce the risk of deterioration of the motor and cognitive condition and the negative psychological effects due to the pandemic and isolation. Telemedicine, and more precisely telerehabilitation, thanks to the use of ICT, can represent a valid option to provide professional assistance to users who cannot follow a therapeutic program in presence, to monitor and safeguard the state health care (Ceravolo et al., 2020; Verduzco - Gutierrez et al., 2020; Tanaka et al., 2020; Noone et al., 2020).

5.3 Telerehabilitation

Over the years, the emerging needs of the population and the rise of new communication technologies have produced a growth in the interest of medicine in this topic; this has resulted in an expansion of the studies that examine this way of providing health services (Peretti et al., 2017). Since the 2000s, further developments in ICT and the widespread use of broadband home connections have made it possible for people with disabilities and healthcare professionals to communicate easily via videoconferencing (Zhou & Parmanto, 2019). In fact, the number of patients assisted through telerehabilitation began to increase from 2007, both thanks to technological growth and thanks to the overcoming of the initial scepticism to which every new technology is subject (Peretti et al., 2017). According to a systematic review by Batsis et al. (2019), telemedicine is viable, sustainable and acceptable in delivering care to older people. Clinicians should consider its use in routine practice to overcome barriers of distance and access to services, while achieving comparable outcomes to traditional interventions. Telemedicine also appears to increase communication and involvement between healthcare professionals, patients and caregivers, especially if conducted in real time via videoconferencing (Orlando et al., 2019). The rapid expansion of telemedicine during the COVID-19 pandemic has been well accepted by most patients and physicians, suggesting the possibility that telemedicine could rapidly spread in the future (Tenforde et al., 2020). In fact, regardless of the emergency period, telemedicine allows to create new opportunities for the improvement of the health service through greater collaboration between the various health professionals and patients.

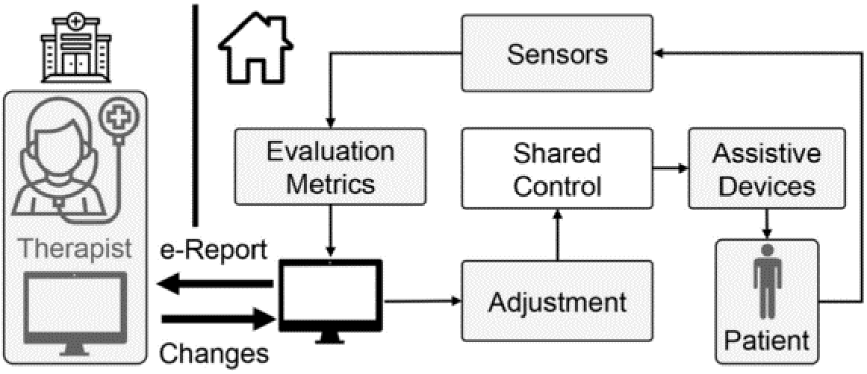

Figure 10. Scheme of remotely monitored telerehabilitation (Manjunatha et al., 2021)

5.3.1 Benefits and barriers of telerehabilitation

Telerehabilitation interventions have been used successfully in the prevention and management of chronic disorders. Among the benefits derived from telemedicine are the reduction of barriers and costs related to travel, the flexibility in the hours dedicated to exercise, the saving of time and the possibility of training more intensively than when it is not possible at a care centre (Van Egmond et al., 2018). This is particularly important for people who otherwise would not be able to access rehabilitation services due to physical, economic or logistical impediments (Zhou & Parmanto, 2019) and for all those who are chronic patients, parents with young children and caregiver of elderly parents (Orlando et al., 2019). Another benefit of telerehabilitation is the reduction in costs associated with the shortening of hospitalization, the saving of resources for patients and clinicians, who, not having to move, can carry out more specialist consultations (Agostini et al., 2015) and therapeutic activities than those that it would be possible to perform presently (Laver et al., 2020). The simultaneous participation of several patients at time is also to be considered a benefit (Amatya et al., 2015). However, the results favouring the use of telemedicine and telerehabilitation are not sufficient to prove its effectiveness in improving the condition of people with disabilities (Zhou & Parmanto, 2019; Appleby et al., 2019). Furthermore, there is currently no proven information on the cost-effectiveness of remote services (Laver et al., 2020).

There are several barriers that can be identified in the literature: I) need for technical requirements to set up a remote therapeutic environment (presence of more or less expensive technological devices, a good internet connection and good audio / video quality) (Kairy et al., 2009 ; Agostini et al., 2015; Peretti et al., 2017; Zhou & Parmanto, 2019); II) Skepticism towards technology (Wang et al., 2019); III) little experience with technology plus multi-comorbidities and sensory, cognitive and age-related deficits in elderly patients (Batsis et al., 2019); IV) lack of technical skills among some practioners and patients, for examples, in knowing how to install systems and solve problems related to ICT (Laver et al., 2020). In fact, telemedicine systems, in order to function, require the human capacity to interact with the technologies used. For the service to be effective, the patient must be trained in its use. A report by the *Istituto Superiore di Sanità - COVID19* (Gabbrielli et al., 2020) suggests some indications, such as simple and intuitive graphic interfaces, simple instructions available in both written and oral format, the professional's first contact by telephone, with the recipient of the service, or with his caregiver.

The patient who, with the appropriate explanations, fails to connect via video call will hardly be able to use a telemedicine service in emergency conditions. Another limiting domain in telerehabilitation is that relating to the data protection and patient privacy, a source of concern in the application of remote healthcare services (Wang et al., 2019; Laver et al., 2020), especially in the case of the asynchronous mode, due to the registration of patient data in special portals (Verduzco - Gutierrez et al., 2020). Insurance-related issues and difficulties in finding effective payment and reimbursement systems for remote service costs were also identified (Tenforde et al., 2017; Tenforde et al., 2020; Contreras et al., 2020). Finally, there is a risk that the remote mode of interaction impairs human contact between practioner and patient. In fact, this modality, by limiting non-verbal expression, modifies the traditional communicative ritual (Peretti et al., 2017).

5.3.2 Predictive factors for the use of technology

The use of technology has become an integral component of people's lives; thus spreading also in the health sector. Several studies have focused attention on predictive factors regarding the use of technology in the elderly, finding that, although they use technology increasingly, they typically have more difficulty than young people in learning how to use new technologies such as computers, the Internet, and smartphone. They also have lower levels of confidence in their computer skills and less computer skills than younger people. Not being properly trained in the use of technology puts the elderly at a disadvantage in terms of independence and understanding its benefits and advantages (Berkowsky et al., 2017).

Czaja et al. (2006) identified the presence of a "digital gap" between the general population and some social subgroups such as ethnic minorities, the elderly and less educated people: all these social realities seem to have less experience with the use of computers and the internet with respect to white, young and/or highly educated individuals. Furthermore, having good self-efficacy is an important predictor for the general use of the technology; it seems that elderly and middle-aged subjects have a lower self-efficacy and a higher level of anxiety (accompanied by a lower interest) than young adults. From this, it is clear that it could be useful to provide, especially for the elderly, an educational program that reduces users' anxiety about technology and facilitates its approach. In general, people with higher levels of anxiety about the use of technology are less likely to adopt the latter, also reporting limited practical experience. The importance of ensuring well-designed and easy-to-use interfaces is therefore emphasized (Czaja et al., 2006).

The variables that influence the acceptance of technology are not necessarily the same between professionals and patients: for example, ease of use of technology is crucial for patients only, while the perceived benefit is for both (Gücin et al., 2015). The optimism and the evaluation that the participants give to their knowledge and cognitive abilities seem to be strongly correlated with the willingness to adopt new technologies. Memory and processing speed are fundamental cognitive skills for a good performance of technology-based tasks, but it is not yet clear whether they are directly related to the predisposition and to use technology. Other important aspects seem to be the perception of the usefulness of technology and the confidence in one's learning abilities (Berkowsky et al., 2017).

5.3.3 Telerehabilitation and disability

In the literature there are studies relating to telerehabilitation interventions applied to a broad spectrum of patients; these represent an approach that has proved to be effective for pathologies such as: stroke and traumatic brain injury (Huijgen et al., 2008, Appleby et al., 2019), multiple sclerosis (Khan et al., 2015; Amatya et al. , 2015; Finkelstein & Liu, 2018); osteoarthritis (De Vries et al., 2017), knee arthroplasty (Jiang et al., 2018), and postoperative in general (Van Egmond et al., 2018), oncological problems (Gehring et al., 2018), respiratory (Lundell et al., 2015) and cardiocirculatory (Dalleck et al., 2011). The elderly population is also represented with problems of various nature and extent (Velayati et al., 2020).

Subsequent studies concern the application of tele-rehabilitation in the COVID-19 context (Contreras et al., 2020; MEDICA, 2020), the satisfaction of stakeholders in the fruition and use of technology-mediated interventions (Orlando et al., 2019) and the application of remote assistance for people living in remote and underserved areas (Zhou & Parmanto, 2019). The effects of tele-rehabilitation on quality of life appear to be promising. In fact, the literature shows that most patients have declared a positive opinion regarding digital interventions administered remotely, some have improved motor performance, language skills and ADL, mental status, and quality of life. Caregivers also benefited and were satisfied. Finally, healthcare professionals seem to have positively welcomed this approach, comparing it in some aspects to the traditional approach, with the advantage of increasing the time dedicated to the patient, reducing the expenditure of time and money (Zhou & Parmanto, 2019; Orlando et al. , 2019).

5.3.3.1 Telerehabilitation in neurological diseases

Studies that address the application of telerehabilitation in the neurological field cover a wide spectrum of pathologies but are mainly based on the rehabilitation pathways of patients with stroke and multiple sclerosis.

In patients with stroke outcomes, remote physiotherapy, when compared with a combination of traditional treatments that do not include the use of technology, show no superior but comparable efficacy. There is good adherence to treatment, similar effects are found in the outcomes of motor functioning, in ADL and in quality of life. Regarding walking, the results are inconclusive (Rintala et al., 2019; Appleby et al., 2019). Other studies have shown comparable results in terms of QoL, patient satisfaction, motor function, balance, and ADL, and it has been shown that costs are reduced in telerehabilitation compared to traditional rehabilitation (Appleby et al., 2019; Caughlin et al., 2020). Stroke patients also declared that they were overall satisfied with the telerehabilitation services, if they were adequately educated for use and there was the possibility of confrontation with the therapist (MEDICA, 2020). Furthermore, thanks to telemedicine, stroke survivors can be followed by a healthcare professional even if they have limited financial or time resources and live in an isolated geographic location (Appleby et al., 2019) or in areas with insufficient rehabilitation services, with the same level of satisfaction (Johansson & Wild, 2011). Finally, telerehabilitation in stroke could also be used for educational purposes and to provide support to caregivers.

As for MS patients, it has been shown that telerehabilitation can facilitate the multidisciplinary management that is necessary for patients with this disease, with the advantage of providing equal access to people who live in geographically remote areas and who are at a physical and economic disadvantage. In general, there seems to be a growing awareness of the effectiveness of telerehabilitation to manage the disease; remote programs have been shown to be useful in improving symptoms, including psychological well-being, motor and cognitive functioning; however, the evidence is still scarce and inconclusive (Khan et al., 2015; Amatya et al., 2015).

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AIMS OF THE RESEARCH

Neurorehabilitation consists in a personalized, multidisciplinary treatment approach designed to simultaneously address impairment caused by nervous system injury, as well as co-occurring motor, psychological and neurocognitive impairments. The neuro-psychological deficits carry the potential to compromise recovery and treatment. Despite its overwhelming impact it is not incorporated in clinical ratings and decision making in the way it should be. In taking charge of the patient, it would be good to consider a biopsychosocial perspective. Biological, psychological (i.e. emotion, thoughts, and behaviours) and social (cultural, socio-economical, socio-environmental) factors, altogether play a substantial role in health and illness; thus, diseases are best understood and treated in terms of a combination of all these factors. Anxiety and depression have varying impacts on health-related Quality of Life (HRQoL) in neurological diseases, as MS and Stroke and this symptomatology negatively affect rehabilitation outcomes and quality of life. Resilience is a construct to consider in these chronic conditions, the patient ability to adapt positively in the face of trauma is potentially a protective factor that help ameliorate patient well-being.

A collaborative approach in neurorehabilitation has the advantage of simplifying co-management of symptoms and detecting when a specific treatment modality may be contraindicated, with the end aim to improve patients' well-being and realize a desired level of functioning. In the past decades, a growing body of evidence have been produced within neuroscience research on motor recovery processes after central nervous system lesions and use-dependent plasticity principles. The adult human brain, even after a damage maintains the abilities to induce cortical reorganization patterns that reflects, at a behavioural level, the acquisition of a motor task.

The most powerful variables which may induce such plasticity are movements themselves, the human brain is capable of significant adaptations depending on the quantity (duration and frequency) and quality (task-specificity) of the proposed interventions, promoting neural reorganization and motor recovery. The brain undergoes plastic modifications (e.g. molecular, cellular and synaptic) in response to our experience; for this motive, the confines between concepts of brain and cognitive reserve should be shortened. Brain reserve refers to individual differences in the structural properties of the brain which could make more resilient to suffer from neurodegenerative and mental diseases. Whereas cognitive reserve refers to the ability of an individual to cope with brain pathology remaining free of cognitive symptoms. This protective factor is thought to allow some individuals to cope with these changes more effectively, and to better maintain cognitive function through more flexible use of cognitive processes or compensatory strategies. Indeed, there is a mounting interest in cognitive reserve that sum up premorbid life of each patient (i.e. educational level, leisure activities, and work activity): it impacts motor rehabilitation outcome and may help in the choice between technological or conventional rehabilitation.

In the last few years, neurorehabilitation has moved from a "bottom-up" to a "top-down" approach. It infers that throughout a task, new "top-down" approaches are being used to stimulate the brain in a more direct way to stimulate plasticity mediated motor re-learning. As opposed to "bottom-up" approaches, which act at the physical level and try to carry about changes at the level of the central neural system. Motor and cognitive systems are strongly associated in humans and thus cannot be separated in neurorehabilitation; all cognitive motor-based rehabilitation devices aim to enhance motor learning and neural reorganization by boosting attention and executive functions related to goal-directed movements. This change of approach has also involved the develop of new technologies, that have been introduced in clinical settings to help restoring functions, that might have a greater positive effect than conventional therapies. These new findings lead to a real paradigm shift in neurorehabilitation research and practice, promising an enhanced motor recovery and better functional outcomes in people who suffer from a brain lesion with beneficial effects on ADLs and quality of life.

An important aspect to consider in neurorehabilitation, is that physiotherapy exercises must be repeated weekly, so in long-term rehabilitation programs, patients could become demotivated. Consequently, patients lose focus on the rehabilitation program, and it loses effectiveness. It is know that rehabilitation results are better when patients are motivated and engaged in the treatment. For example, in robotic interventions, the system robotic assistance allows patients to reduce their effort to actively participate during training, whereas video games therapy increases active participation as it not only provides patients with an external feedback about their motor performance, but can also increase the overall motivation and engagement, thus physical activity, during training using game-like scenarios. It is therefore useful to find tricks to make any kind of treatment involving and stimulating for the patient.

While there have been enormous gains in knowledge about rehabilitation technique in recent decades, less attention has been paid to long-term management of neurological patients. This theme needs to be addressed, since there are issues faced on a daily basis that severely affect patient quality of life and may be ameliorated with appropriate management. Neglecting the long-term care of the patient could involve risk of a slow and progressive loss of functional reserve with consequent loss of autonomy in daily life and greater risk of adverse events (e.g. falls). The goal should be to achieve the highest possible improvement in the quality of life in order to make life expectancy coincide with active life expectancy.

Finally, in the context of the COVID-19 pandemic, telemedicine has proved to be a necessity in order to be able to remotely monitor patients, guaranteeing prompt intervention, in real time and decreasing the chances of spreading the infection. Despite the disadvantages of remote rehabilitation, the application of remote communication systems in the rehabilitation field could be defined as a new model of care and help improve health care by meeting the needs of the patient.

This dissertation document comprises separate, but related, studies that highlight the relation between psychological and cognitive elements and motor performance and raise several practical implications for designing effective motor training programs, considering its mutual influences.

To address this overarching aim, five specific aims were developed:

1. To test efficacy of cerebellar Transcranial Direct Current Stimulation combined with a Task-oriented circuit training in MS patients with balance and mobility impairments. Secondly, evaluate their effects on mood and in executive function abilities.
2. To test the efficacy of a commercially available video game therapy (Xbox Kinect) on mobility and dual-tasking in ambulatory people with MS in comparison to a standardised balance platform training. Secondly, describe their impact in the health-related quality of life, the cognitive functioning and psychological wellbeing.
3. To identify the attentional deficits in a sample of subacute stroke patients and evaluate the effects of four weeks Action Observation Training on attention and patients' engagement and their influence on motor recovery.
4. To test the disability and HR-QoL in subacute stroke at the end of treatment consisting on intensive conventional therapy or unilateral, proximal arm robot-assisted therapy combined with hand functional electrical stimulation. Secondly, to identify demographic and clinical factors that influence disability and HR-QoL at short-term (6 months) and long-term follow-up (6 years).
5. To assess the feasibility and acceptability of a telerehabilitation program during the COVID-19 lockdown in a sample of adult patients with physical disabilities. Secondly, to identify the potential predictors (i.e. demographic, clinical, and psychological variables) of successful participation in telerehabilitation programs.

PUBLISHED AND SUBMITTED PAPERS

1. Cerebellar tDCS combined with a task-oriented circuit training doesn’t improve motor function in people with Multiple Sclerosis: a pilot randomized control trial
2. Video Game Therapy on mobility and dual tasking in Multiple Sclerosis: study protocol for a randomised controlled trial
3. Action Observation Training for Upper Limb Stroke Rehabilitation: The Role of Attention and Engagement
4. The Multifactorial Nature of Disability and Health-related Quality Of Life after Stroke: A 6-Years Follow-Up Study
5. Telerehabilitation in italy during the COVID-19 lockdown: a feasibility and acceptability study

CEREBELLAR tDCS COMBINED WITH A TASK-ORIENTED CIRCUIT TRAINING DOESN'T IMPROVE MOTOR FUNCTION IN PEOPLE WITH MULTIPLE SCLEROSIS: A PILOT RANDOMIZED CONTROL TRIAL.

ABSTRACT

Introduction: Balance and mobility impaiments are frequent in people with multiple sclerosis, probably due to cerebellar disfunctions. Task-oriented approach promotes physical function and cerebellar transcranial direct current stimulation (ctDCS) applied during training seems to boost effects of rehabilitation through modulation of cerebellum-brain inhibition.

Aim: To test efficacy of cerebellar stimulation combined with motor training on mobility and balance in people with multiple sclerosis

Methods: Double-blind pilot randomized clinical trial on 16 subjects, randomly assigned to receive real- or sham-ctDCS and task-oriented training daily over two weeks. Functional mobility, balance, walking performance and quality of life were tested before and after treatment and at two-weeks follow-up. Effects of cerebellar stimulation on psychological and executive functions were recorded.

Results: Walking performance, balance and quality of life improved for both groups at post-treatment assessment and improvements were maintained at 2-weeks follow up. A two-way ANOVA revealed a significant time effect for balance and walking performance. A significant interaction effect of time–treatment was found for motor aspects of quality of life assessment on group of patients who received real-ctDCS.

Conclusions: task-oriented training improves balance and mobility in people with multiple sclerosis but ctDCS doesn't boost motor training effects.

Keywords: multiple sclerosis, mobility, balance, tDCS, task-oriented, cerebellum

Highlights

- Motor impairments are frequent in people with multiple sclerosis
- Cerebellum has a crucial role on balance and motor control
- Cerebellar stimulation combined with motor training influences motor function

1.1 Introduction

People with multiple sclerosis (PwMS) are frequently affected by motor impairments (ambulation, balance, mobility). It has been shown how 80% of them experience a loss of ambulation function that accurses over time (Feinstein & Freeman, 2015). Walking impairments have a high negative impact on personal activities; they are associated with loss of physical quality of life and increased risk of fall (Delgado-Mendilívar, 2005; Pfaffenberger et al., 2006; Gunn et al., 2013). Several studies showed the benefits of physical therapy on walking functions (Paltamaa et al., 2012; Khan et al., 2017; Edwards et al., 2017; Motl et al., 2017). There is an increasing body of evidence demonstrating that the human adult brain is capable of significant adaptations providing that the quantity (duration and frequency) and quality (task-specificity) of interventions are appropriate to promote neural reorganization and motor recovery (Jang et al., 2003; Kleim et al., 2008).

Task-oriented circuit training (TOCT) is an example of intense task-specific intervention to promote mobility and balance. It is constituted by a set of working stations that reflect the physical activities the subject performs daily (walking, climbing stairs, maintaining balance) to promote learning and walking function (Straudi et al., 2014). In addition to the choice of functional motor tasks, the main characteristic of this rehabilitative intervention is the exercise intensity that, compared to a conventional approach, is closer to the number of repetitions needed to achieve and maintain motor learning of these movements (Lang et al., 2009; Straudi et al., 2016).

The cerebellum has a crucial role on balance and motor control, integrating primary motor cortex (M1) activity through specific pathways (Galea et al., 2009; Ferrucci et al., 2016; Grimaldi et al., 2016). The cerebellum is also activated in adaptive motor learning circuits (Hamada et al., 2012; Celnik, 2015). Furthermore, several studies demonstrated its role in cognition, emotions, and behavior (Reeber et al., 2013; Strick et al., 2009). Cerebellum dysfunctions seem to be related to many neurological disorders as dystonia and essential tremor in Parkinson Disease and cerebellar ataxia (Ferrucci et al., 2016). Moreover, fMRI studies showed a positive correlation between gait recovery and contralesionally cerebellum activity in stroke patients (Celnik, 2015).

In PwMS, the cerebellum could be the main contributor to balance and mobility impairments (Feinstein et al., 2015). Therefore, cerebellar activity modulation might play an essential role in developing potential rehabilitation strategies for PwMS. The cerebellar activity involved in motor learning may be modulated through non-invasive brain stimulation, especially for restoring balance and gait. Transcranial direct current stimulation (tDCS) can modulate cerebellar excitability in humans. In particular, cathodal tDCS decrease and anodal tDCS increase cerebellum-brain inhibition (CBI) (Galea et al., 2009; Ferrucci et al., 2016). Increased CBI mediated by Purkinje cells through dentato-thalamocortical pathways results in plasticity modifications of the primary motor cortex (Grimaldi et al., 2016). Furthermore, non-invasive cerebellar stimulation has been a valuable option in increasing mobility and balance in subacute stroke survivors, representing the cerebellum as an alternative target of brain stimulation for primary motor areas (Koch et al., 2019).

The loss of M1 plasticity with the progression of axonal damages in PwMS could contribute to the development of disease and the increasing of disability (Reddy et al., 2000).

Based on this background, we hypothesized that combined cerebellar tDCS (ctDCS) with TOCT could improve locomotor function and balance in PwMS and mild to moderate gait disabilities. Furthermore, since it has been reported positive effects of both tDCS and physical activity on psychological well-being, we investigate their effect on the level of depression and anxiety (Cooney et al., 2013; Kuo et al., 2017). Given the role of the cerebellum in executive functioning, we evaluated the effects of ctDCS on a Go/NoGo task, assuming an improvement in response inhibition (Mannarelli et al., 2020).

1.2 Methods

This exploratory pilot study was a double-blind, randomized clinical trial to test the efficacy of cerebellar tDCS combined with task-oriented circuit training (TOCT) on mobility and balance outcomes in PwMS. This study has been reviewed by the Ferrara University Hospital Ethics Committees and registered on clinicaltrials.gov (NCT01883843). Written informed consent was obtained before all procedures.

Inclusion criteria were as follows: (i) male and female aged >18 years, (ii) diagnosis of MS (primary or secondary progressive, relapsing-remitting), without relapses in the preceding three months, (iii) unassisted walking with an Expanded Disability Status Scale (EDSS) score between 4 and 5.5. Exclusion criteria were as follows: (i) impaired cognitive functioning (score less than 24 on the Mini Mental Status Examination); (ii) intracranial metal implants that can be stimulated, incorrectly positioned, or overheated by the electric current; (iii) other neurological or psychiatric disorders; (iv) severe cardiopulmonary, renal, and hepatic diseases; (v) pregnancy.

All patients matching inclusion criteria were randomized using an online program (http:// www.randomization.com/). The random list was managed by an administrator external to the research groups to prevent selection bias.

Patients enrolled were allocated in two treatment groups: the experimental group received real-ctDCS and TOCT; the control group received sham-ctDCS and TOCT. The treatment group allocation was blinded for patients, investigators, physical therapists and medical doctors involved in the study. Both groups received ten sessions (Monday-Friday) of combined treatments over two weeks; each session lasted 2 hours.

Task-Oriented Circuit Training (TOCT)

TOCT protocol is applied to a group of 3 subjects. Every subject has to exercise in six different workstations for 5 minutes in each one (3 minutes of exercises and 2 minutes of rest) supervised by a physiotherapist. During each session, the patient has to complete two laps that took about 60 minutes (6 workstations × 5 minutes × two laps), with 10 minutes of rest after each lap. During the rest periods, subjects were invited to stretch their muscles. In addition, every patient walked on the treadmill for 30 minutes, including rests if necessary. Further details on the training protocol are available elsewhere (Straudi et al., 2014).

Cerebellar Transcranial Direct Current Stimulation (ctDCS)

The direct current was delivered through a pair of sponge electrodes with a surface of 35 cm2 (7 × 5), soaked in saline solution. It was generated by a constant current stimulator with rechargeable batteries (Brainstim, EMS, Italy). The anode was placed on the right cerebellar cortex, 3cm lateral to the inion (Ugawa et al., 1995). The reference electrode was placed on the right buccinators muscle. This continuous stimulation lasted 15 minutes for the experimental group, with an intensity of 2 mA during the first TOCT lap. For the control group who received sham ctDCS, the current was delivered for only 30 seconds, and then discontinued, but the tDCS apparatus was left in place for the same time as real ctDCS (15 minutes). This procedure has been suggested as an effective blinding method in parallel clinical trials of tDCS (Gandiga et al., 2006; Brunoni et al., 2014). A tDCS side-effects questionnaire (headache, neck pain, burning, redness and/or itching at the stimulation site) was administered after each session to both groups of patients.

Procedures

Subjects were evaluated before (T0) and after treatment (T1) and at two-weeks follow-up (T2) using both functional tests (gait speed, walking endurance, mobility, balance) and self-reported questionnaires for fatigue, walking ability and health-related quality of life. The assessment and treatment were delivered by two different physical therapists to ensure the blinding of evaluators. The primary outcome was functional mobility assessed using the Timed Up and Go test (TUG) (Sebastião et al., 2016). The Figure of-Eight Walk test (F8W) was used to assess walking performance (Wong et al., 2013). Gait, balance, and fall risk were evaluated using the Dynamic Gait Index (DGI) (Forsberg et al., 2013). Impact of MS on walking ability and health-rated quality of life was assessed using the Multiple Sclerosis Walking Scale – 12 (MSWS-12) and the 36-Item Short-Form Health Survey questionnaire (SF-36) respectively (Hobart et al., 2003; Sehanovic et al., 2020). The severity and behavioral characteristics of depression and anxiety were evaluated using the self-report questionnaires Beck Depression Inventory – Second Edition (BDI-II) and State-Trait Anxiety Inventory (STAI-Y), respectively (Sica & Ghisi, 2007; Santangelo et al., 2016). Effects of ctDCS on executive functions were evaluated using the subtest "Go/Nogo" of the Test Battery for Attention (TAP), a response inhibition task (Zimmermann & Fimm, 2002; Tinnefeld et al., 2005). A sequence of five squares with different patterns appears on the screen, two of these squares are defined as target stimuli. Test aims to respond to target stimuli as accurately and as fast as possible while ignoring the non-target stimuli. The task duration was 2 minutes.

Statistical analysis

Descriptive statistics (mean, standard deviation) described the sample at T0, T1, T2. Baseline characteristics and clinical tests were compared among groups to confirm the quality of randomization using the Wilcoxon rank or Pearson's Chi-Square test. A repeated-measures ANOVA analysis (within-group factor: TIME; between-group factor: TREATMENT) was conducted to detect main effects for treatment and time. Statistical analysis was performed using STATA 13.1 software. Statistical significance was set to $p < 0.05$.

1.3 Results

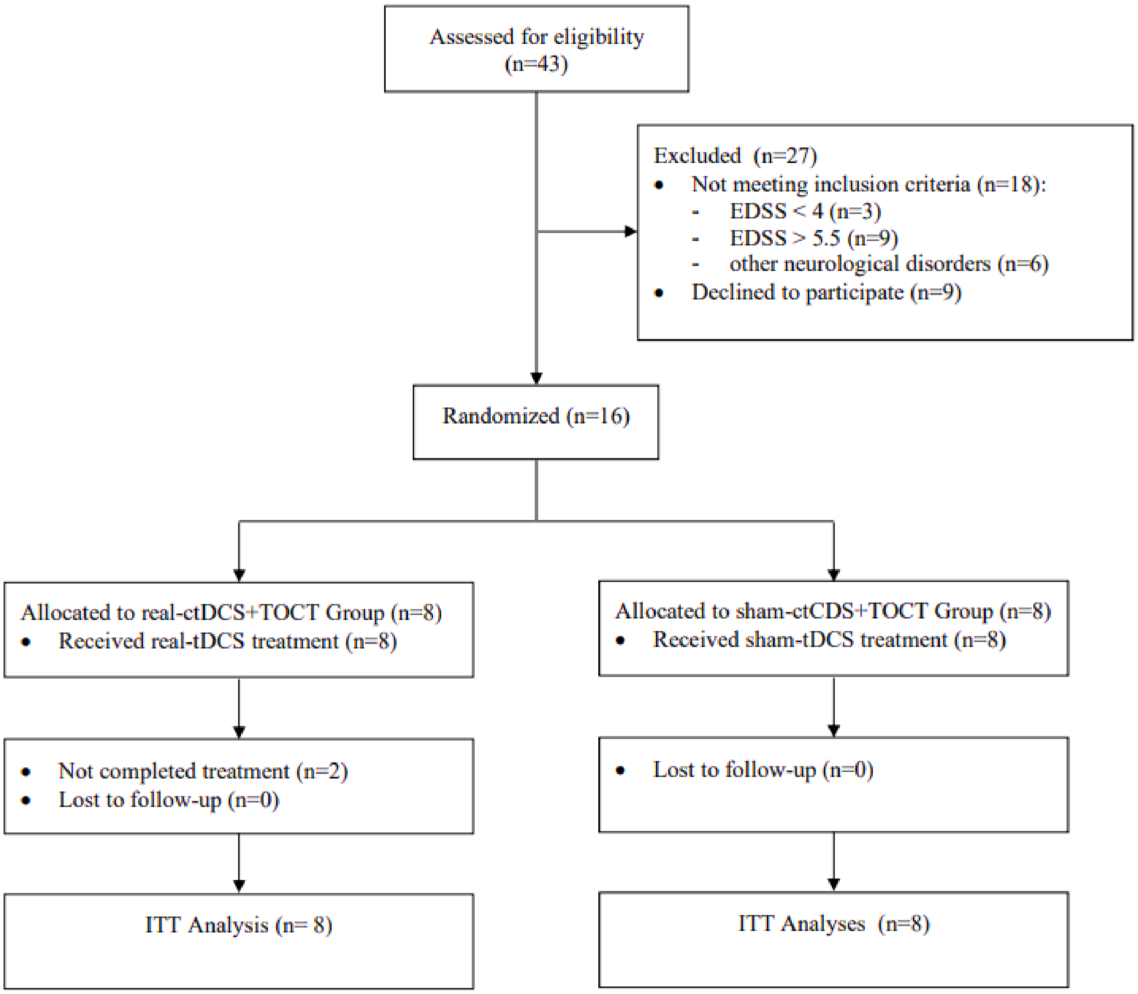
Forty-three PwMS were screened for this study, and 16 were enrolled (mean age = 53.7 ± 13 years, eight males and eight females) at Ferrara University Hospital. The two groups were similar in demographic and clinical characteristics at the baseline (*Table 1*). Two subjects allocated to the experimental group didn't complete the combined treatment for personal issues unrelated to the treatment received. The CONSORT flow diagram of the study is reported in *Figure 1*.

Table 1. **Demographic and clinical characteristics of the sample**

	Real-ctDCS + TOCT (*n* = 8)	Sham-ctDCS + TOCT (*n* = 8)	Total (*n* = 16)	*p*
Age (years)	55.25 (15.15)	52.13 (11.31)	53.69 (13.01)	0.67
Sex: M/F	4/4	4/4	8/8	
MS onset (years)	11.13 (6.99)	11.13 (9.95)	11.13 (8.31)	0.67
MS subtypes: RR/PP/SP	3/4/1	3/3/2	6/7/3	
EDSS	4.69 (0.53)	4.5 (0.71)	4.59 (0.61)	0.47
TUG baseline	9.92 (2.39)	8.88 (1.9)	9.39 (2.16)	0.34
F8W baseline (sec)	9.37 (2.68)	8.36 (3.06)	8.87 (2.83)	0.25
DGI baseline	16 (2.98)	16.75 (1.98)	16.38 (2.47)	0.59
MSWS-12 baseline	59.13 (16.17)	69.95 (13.61)	64.54 (15.48)	0.23
SF-36-PCS baseline	41.38 (5.34)	34.63 (8.23)	38 (7.55)	0.10
SF-36-MCS baseline	50.75 (9.19)	50.38 (11.19)	50.56 (9.89)	0.87
STAI-Y1baseline	32.17 (15.31)	29.75 (6.85)	31.2 (12.5)	0.67
STAI-Y2 baseline	33.67 (11.51)	34 (12.02)	33.8 (11.04)	0.83
BDI baseline	7 (7.48)	9.5 (8.06)	8 (7.38)	0.59
Go/Nogo correct baseline	22.88 (1.64)	21.75 (3.28)	22.31 (2.57)	0.87
Go/Nogo RTs baseline (msec)	602.79 (56.99)	581.13 (50.27)	591.96 (53.11)	0.29

* ctDCS = cerebellar transcranial Direct Current Stimulation; TOCT = Task Oriented Circuit Training; *n* = number; SD = standard deviation; M/F = male/female; MS = multiple sclerosis; RR = relapsing-remitting; PP = primary progressive; SP = secondary progressive; EDSS = Expanded Disability Status Scale; TUG = Timed Up and Go test; F8W = Figure of-Eight Walk test; DGI = Dynamic Gait Index; MSWS-12 = Multiple Sclerosis Walking Scale – 12; SF-36 = 36-Item Short Form Health Survey questionnaire (PCS = Physical Component Summary; MCS = Mental Component Summary); STAI = State-Trait Anxiety Inventory (Y1 = trait anxiety; Y2 = state anxiety); BDI = Beck Depression Inventory; RTs = Reaction Times; *p* = difference between real-ctDCS + TOCT group and sham-ctDCS + TOCT group.

Figure 1. CONSORT flow diagram



No statistically differences were found between groups on functional mobility. Walking performance and balance function improved for both groups at post-treatment assessment. Improvements were maintained at 2-weeks follow up, as shown by F8WT and DGI scores (*Table 2*). The results of MSWS-12 and SF-36 showed improvements in both groups for all the evaluations. (*Table 2*).
A two-way ANOVA revealed a significant time effect for most outcome measures (F8W, DGI, MSWS-12). A significant interaction effect of time–treatment (F = 3.12, df = 2,26; $p < 0.05$) was found for Physical Component Summary of SF-36 on group of patients who received real-ctDCS (*Table 3*). The two groups did not differ on measures of response inhibition, neither for accuracy nor for reaction times: both of them improved at the end of treatment. The results of ctDCS Adverse Effects Questionnaires are reported in *Table 4*.

Table 2. Changes in outcome measurements (mean ± SD)

	Changes at T1		Changes at T2	
	Real-ctDCS + TOCT	Sham-ctDCS + TOCT	Real-ctDCS + TOCT	Sham-ctDCS + TOCT
TUG (sec)	0.03 ± 1.13	-0.48 ± 0.48	0.28 ± 0.75	-0.54 ± 1.02
F8W (sec)	-0.20 ± 0.74	-1.09 ± 2.15	-0.82 ± 1.18	-1.23 ± 2.00
DGI	1.75 ± 2.66	2.75 ± 2.49	0.75 ± 2.38	1.62 ± 2.33
MSWS-12	-9.80 ± 7.94	-10.19 ± 5.16	-18.11 ± 10.96	-21.09 ± 15.84
SF-36-PCS	3.88 ± 4.97	2.38 ± 4.34	2.88 ± 4.36	0.25 ± 5.65
SF-36-MCS	2.13 ± 5.30	4.63 ± 10.70	-0.38 ± 3.62	4.25 ± 10.09
STAI-Y1	0.33 ± 1.57	8.50 ± 6.55	-0.96 ± 5.66	-0.08 ± 3.17
STAI-Y2	0.16 ± 0.80	1.50 ± 0.56	0.33 ± 2.46	3.67 ± 3.01
BDI	1.50 ± 0.10	-1.50 ± 0.54	1.40 ± 1.29	0.17 ± 3.09
Go/Nogo correct	0.38 ± 0.74	2.13 ± 2.99	0.50 ± 1.93	2.13 ± 3.27
Go/Nogo RTs	-32.95 ± 76.29	-8.51 ± 5.30	-33.79 ± 78.36	-54.53 ± 35.94

*ctDCS = cerebellar transcranial Direct Current Stimulation; TOCT = Task Oriented Circuit Training; SD = standard deviation; TUG = Timed Up and Go test; F8W = Figure of-Eight Walk test; DGI = Dynamic Gait Index; MSWS-12 = Multiple Sclerosis Walking Scale – 12; MSIS-29 = Multiple Sclerosis Impact Scale – 29 (phy = physical domain; psy = psychological domain); SF-36 = 36-Item Short Form Health Survey questionnaire (PCS = Physical Component Summary; MCS = Mental Component Summary); STAI = State-Trait Anxiety Inventory (Y1 = trait anxiety; Y2 = state anxiety); BDI = Beck Depression Inventory; RTs = Reaction Times.

Table 3. Analysis of variance for outcome variables

	Group Effect		Time Effect		Interaction (Time x Group)	
	F (1.14)	*p*	F (2.26)	*p*	F (2.26)	*p*
TUG	2.69	0.12	2.15	0.10	2.50	0.07
F8W	2.01	0.17	3.55	0.02	0.62	0.60
DGI	2.14	0.16	6.07	0.00	0.54	0.65
MSWS-12	0.68	0.42	21.07	0.00	2.11	0.11
SF-36-PCS	0.29	0.60	2.03	0.12	3.12	0.03
SF-36-MCS	0.53	0.47	2.81	0.05	0.51	0.67
STAI-Y1	0.00	0.99	2.88	0.08	1.81	0.20
STAI-Y2	0.06	0.81	0.87	0.44	2.25	0.14
BDI	0.45	0.52	0.03	0.96	0.60	0.56
Go/Nogo correct	0.00	1.00	3.87	0.03	1.68	0.20
Go/Nogo RTs	0.51	0.48	5.49	0.00	1.44	0.25

*TUG = Timed Up and Go test; F8W = Figure of-Eight Walk test; DGI = Dynamic Gait Index; MSWS-12 = Multiple Sclerosis Walking Scale – 12; SF-36 = 36-Item Short Form Health Survey questionnaire (PCS = Physical Component Summary; MCS = Mental Component Summary); STAI = State-Trait Anxiety Inventory (Y1 = trait anxiety; Y2 = state anxiety); BDI = Beck Depression Inventory; RTs = Reaction Time

Table 4. Frequencies of patients reported side effects after stimulation, n (%)

	Real-ctDCS (*n* = 8)	Sham-ctDCS (*n* = 8)	Total (*n* = 16)	*p*
Tingling	4 (50)	3 (37.5)	7 (43.75)	0.63
Skin redness	5 (62.5)	-	5 (31.25)	0.01
Headache	-	2 (25)	2 (12.5)	0.14
Trouble to concentrate	1 (12.5)	1 (12.5)	2 (12.5)	1.00
Sleepiness	-	1 (12.5)	1 (6.25)	0.32
Pain in the site of stimulation	1 (12.5)	-	1 (6.25)	0.32
Mood fluctuations	1 (12.5)	-	1 (6.25)	0.32

*ctDCS = cerebellar transcranial Direct Current Stimulation; p = difference between real-ctDCS group and sham-ctDCS group.

1.4 Discussion

Our results revealed that TOCT effectively ameliorates balance and mobility in a convenience sample of PwMS, but ctDCS doesn't boost motor training effects. A previous pilot study showed beneficial effects of TOCT on walking ability and health-related quality of life, two domains frequently affected in PwMS (Straudi et al., 2014). Anodal ctDCS seems to have no additional benefits in our sample. To our knowledge, the current study is the first to investigate the combined effect of ctDCS and motor training in PwMS. Many studies have shown enhanced cerebellum-dependent motor learning in healthy subjects using comparable ctDCS montage and stimulation parameters (Jayaram et al., 2012; Cantarero et al., 2015; Galea et al., 2011; Spampinato et al., 2017). ctDCS has been used to increase cerebellar activity and facilitate the cerebellum and the entire related network; Billeri et al. sustained that the effects of this approach would depend on the residual functional reserve of the cerebellum (Billeri & Naro, 2021). We can assume that MS-related brain damage may have reduced the impact of ctDCS on motor function. For this reason, in people with neurological disorders and variable lesions distribution, a pre-stimulation assessment could be helpful to identify patients who better respond to ctDCS and define the best patient-tailored stimulation protocol. The adoption of brain resting-state measures (ie. EEG) as biomarker of response to ctDCS could help delineate good versus poor candidates to receive this stimulation protocol. Another possible explanation of our results is that a ceiling effect on motor recovery is reached by TOCT alone, making it difficult to find further improvements due to tDCS.

The tDCS effect seems to be task-dependent, and its role on motor learning is based on the state of cortical activation at the stimulation time (Bortoletto et al., 2015). We can speculate that more challenging tasks as TOCT's activities require a greater activation of the primary motor cortex in PwMS than healthy subjects engaged in relatively standardized motor tasks like walking on a split-belt treadmill or complete finger tracking training (Jayaram et al., 2012; Summers et al., 2018). Generally, tDCS effects are polarity-dependent, and anodal tDCS increases neuronal excitability (Nitsche & Paulus, 2000). However, tDCS may either facilitate or inhibit motor learning based on the state of cortical activation at the time of stimulation. In our case, ctDCS was combined with a task-oriented motor training that increases cortical excitability, hindering facilitatory effect of tDCS (Bortoletto et al., 2015).

Controversial is the identification of the exact timing of stimulation to optimize the effects of motor training. Many studies try to find the window during which brain stimulation should be applied to increase brain plasticity, without consensus between them (Giacobbe et al., 2013). Cabral et al. sustained that the overlapping effect of non-invasive brain stimulation and motor training may reduce the impact of a single treatment on the motor outcome (Cabral et al., 2015). Similar results were found by Summers et al., who recorded decreased corticospinal excitability following application of anodal ctDCS during motor training (Summers et al., 2018).

Both motor training and brain stimulation seem to promote neuroplastic changes in the human cortex, but their combination may reduce the effects of the single treatment on motor outcome (Cabral et al., 2015). This possible explanation, although not directly linked to cerebellum stimulation, may justify our findings. For this reason is essential to choose a trial design that considers the appropriate temporal and spatial relationship between the combined treatments (Cabral et al., 2015; Straudi et al., 2018).

At least, the identification of the best cerebellar subregion that plays an important role in conditioning motor processes can be crucial. The anterior cerebellum is more involved in motor performance control (Stoodley & Schmahmann, 2010; Kern et al., 2011; D'Ambrosio et al., 2017). However, tDCS targeting the anterior sensorimotor cerebellum proved to be not the best ctDCS montage to modulate motor function (Rice et al., 2021). Furthermore, using this stimulation protocol, the cerebellum motor area is too far from the scalp surface to be stimulated (Grimaldi et al., 2016): this could explain our motor results outcomes. For this reason, different electrode positioning should be tried in combination with motor training.

The group treated with real-ctDCS showed improvements in psychological aspects of health-related quality of life, but the effects were evident only at post-treatment evaluation. Electrodes position in our ctDCS set up stimulates the posterior and inferior aspects of the cerebellum closest to the skull (Galea et al., 2009; Grimaldi et al., 2016). The posterior lobe plays a role in modulating cognitive performance, and lesions of this cerebellum area have been observed in patients with neuropsychiatric impairments (Schmahmann et al., 2007; Stoodley et al., 2010; D'Ambrosio et al.; 2017). Our findings contrast with a recent meta-analysis that showed how motor performance was significantly more affected than cognitive performance following ctDCS in healthy subjects (Oldrati & Schutter, 2018) the presence of neurological disorders may influence the effects of stimulation on cerebellar areas (Middleton & Strick, 2001; Ramnani, 2006; Stoodley & Schmahmann, 2010).

The novelty of our study lies in the hypothesis of combining cerebellar stimulation with an intensive and task-oriented rehabilitation programme. Although preliminary studies highlighted the importance of this type of rehabilitation in PwMS (Chisari et al., 2014; Lehmann et al., 2020), the addition of ctDCS seems to have no additional effects on motor aspects. Conversely, physical health-related quality of life was superior after this non-invasive brain stimulation approach.

No major side effects were reported after either anodal or sham ctDCS, only mild side effects equally distributed among anodal and sham conditions. Only patients who received anodal ctDCS shown skin redness under site of stimulation which resolved few minutes after the end of stimulation. This in line with previous studies on tDCS in PwMS (Ayache et al., 2020; Hsu et al., 2021).

Our pilot study has several limitations. Firstly, our small sample didn't allow us to determine the efficacy of cerebellar stimulation on motor and non-motor outcomes; secondly, the level of motor impairment was probably too mild to highlight the clinical improvement in the recruited sample; finally, outcome measures we used were not sensitive enough to discriminate walking function or balance impairment in our sample. Future directions: (i) to conduct a large RCT trial to better investigate the role of ctDCS on the motor outcome; (ii) to better explain effects of ctDCS on M1 and role of CBI on the motor function it would be necessary to add cortical function parameters (i.e. EEG, transcranial magnetic stimulation).

1.5 Conclusions

This pilot study assessed the preliminary effects of combining cerebellar stimulation and an intensive and task-oriented rehabilitation programme in PwMS and unassisted walking. Our main findings revealed that TOCT is effective in improving balance and mobility and that ctDCS may boost the effects of motor training on the perceived quality of life. Although positive effects on mobility and the absence of adverse effects following the combined treatment, this pilot study cannot draw definitive conclusions and further studies need to verify our results.

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VIDEO GAME THERAPY ON MOBILITY AND DUAL TASKING IN MULTIPLE SCLEROSIS: STUDY PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL

ABSTRACT

Introduction: Multiple sclerosis (MS) is one of the major causes of disability in young adults and affects mobility, compromising daily living activities and participation in social life. Cognitive domain is also frequently impaired in people with MS (PwMS), particularly the capacity to perform dual-task activities. Impaired cognitive processing abilities need to be treated, and motor and cognitive aspects need to be considered together. Recently, video game therapy (VGT) has been used in rehabilitation to improve motor outcomes and cognitive processing speed. The aim of this study is to test the efficacy of commercially available VGT on mobility and dual tasking in PwMS compared with standardised balance platform training (BPT).

Methods and analysis: This will be a parallel-assignment, double-blinded, randomised control trial. Forty-eight (24 per arm) PwMS with Expanded Disability Status Scale 4–5.5 will be randomly assigned to receive 1 hour training session over 4 weeks (three sessions/week) of either: (1) VGT on commercial video game console to train balance and mobility-related activities or (2) BPT to perform balance, postural stability and weight-shifting exercises with and without visual feedback. The same assessor will evaluate outcome measures at points: before and after the 12 training sessions and at 3 months of follow-up. The primary outcome will be functional mobility, assessed by the Timed Up and Go test. We will also evaluate gait, risk of fall, fatigue and health-related quality of life as well as cognitive and psychological aspects (depression, anxiety and attentional performance) and stability through posturographic evaluation. Dual-tasking assessment will be performed combining posturographic and neuropsychological tests. Data analysis will be performed to compare the efficacy of the two treatments.

Ethics and dissemination: Ethical approval have been granted from the local Ethics Committee. Study results will be communicated through high-quality journals and national and international conferences.

Trial registration number: NCT03353974

Strengths and limitations of this study

- This trial will use objective evaluation as a posturographic assessment to test balance and dual tasking
- Motor and cognitive outcomes will be assessed separately and in association.
- Results from this trial will need a larger sample to be confirmed.
- This study protocol includes only young subjects (aged under 60) with good comprehensive functioning.
- This study does not analyse long-term effects (over 3 months).

2.1 Introduction

Multiple sclerosis (MS) is characterized by multifocal inflammatory demyelinated plaques distributed over time and space within the central nervous system (CNS). It affects approximately 1.3 million people worldwide and is a major cause of chronic neurological disability in young adults aged 18–50 years (World Health Organization, 2008; Khan & Amatya, 2017). Deficits in balance control and cognition are prevalent impairments in people with MS (PwMS) (Cameron & Nilsagard, 2018), even at an early stage and without clinical disability (Martin et al., 2006). Previous studies have reported that 30%–63% of PwMS experience a fall event between 1 and 12 months since the onset of the disease (Prosperini et al., 2013). Balance maintenance is a complex task that depends on the continuous flow of proprioceptive information from the muscles, tendons, joints, skin, vestibular and visual systems toward the CNS (Cameron & Nilsagard, 2018). In PwMS, the extended damage caused in the CNS leads to a decreased ability in integrating the afferent proprioceptive information, thus negatively influencing postural response and the capability to maintain balance safely (Cameron & Lord, 2010; Prosperini et al., 2013). Balance impairment can consistently limit the activities of daily living and the active participation in social life.

Cognitive impairment is various among PwMS, with current prevalence rates ranging from 43% to 70% (Chiaravalloti & DeLuca, 2008). The following cognitive domains are frequently impaired: memory processing speed, attention/concentration and executive functioning (Giazkoulidou et al., 2019). Cognitive impairments are associated with reduced functional status in MS. They have a deleterious impact on the individual's personal, occupational and social functioning and the comprehensive quality of life (Chalah & Ayache, 2017). The role of cognitive functioning on motor performance and balance control is widely known (Saverino et al., 2016). However, the effects of impaired cognitive processes on balance efficacy have not been extensively investigated in PwMS (Negahban et al., 2011). Besides, the comprehensive link between attention and motor-action has been supported by several studies (Song, 2019). Selective attention allows the execution of a correct motor response by selecting relevant information between the task and the distractors, and it is essential for action planning. Concerning the cognitive–motor interference, this relation is directly measurable by the dual- task cost, (Leone et al., 2015; Chamard Witkowski et al., 2019) investigated in PwMS through the Stroop Test (Ruggieri et al., 2018). Dual-task performance is the capacity to do two tasks simultaneously, particularly motor and cognitive tasks. The subject's attention is drawn to an external source of attention while the primary task is ongoing, resulting in cognitive–motor interactions (Sosnoff et al., 2017). Concerning the constrained action hypothesis, this attentional change may lead motor systems to react automatically, thus increasing the performance effectiveness (Ghai et al., 2017). The processing capacity required for doing dual-task activities may be affected by cognitive impairments (Rooney et al., 2020). In subjects with neurological disorders, such as PwMS, the ability of doing a motor task simultaneously to a cognitive one is frequently affected (Ghai et al., 2017).

It is plausible that motor deficits enhance the cognitive demands necessary to execute functional movements, and the concurrent performance of tasks may exceed cognitive processing abilities (Mulder et al., 2002). Considering the strong impact of dual tasking on activities of daily living (ADL) (Chiaravalloti & DeLuca, 2008), rehabilitative treatment does not have to consider the motor and cognitive aspects separately.

In recent years, active video games technologies have begun to be used as a treatment tool in rehabilitation given their low cost, high portability, off-the-shelf nature and ability to deliver engaging, high-repetitive, task-oriented, standardised, active learning therapies (Laver et al., 2017). Moreover, PwMS defined gaming experience as fun, challenging and self-motivating, critical elements for successful motor learning (Forsberg et al., 2015). Active video games' multisensory feedback provided to patients may potentiate the use-dependent plasticity processes in the sensorimotor cortex, promoting functional recovery (Maggio et al., 2019). Furthermore, combined training of cognitive and motor abilities in constantly changing virtual environments is particularly suited to address dual-tasking as required for the constantly changing situations of everyday life (Schaeffer et al., 2019).

The evidence of interactive video game therapeutic exercises for improving balance and motor functions in PwMS were inconclusive, even if few studies showed a possible positive effect on balance and cognitive functions such as processing speed (Brichetto et al., 2013; Parra-Moreno et al., 2018; Pitteri et al., 2020; Bove et al., 2021). Furthermore, patients' motivation seems to be capable of being increased during active video game rehabilitation, allowing patients to exercise more consistently (Maggio et al., 2019). All previous studies did not investigate the effects on motor and cognitive functions simultaneously, particularly when compared with conventional instrumental balance training.

Aims

This study aims to test the efficacy of a commercially available video game therapy (VGT) (Xbox Kinect) on mobility and dual-tasking in ambulatory PwMS in comparison to a standardised balance platform training (BPT).
We hypothesise that augmented feedback during VGT, in terms of intensity and type, would activate the cognitive components of motor learning more effectively than BPT. Moreover, a challenging and engaging approach contributes to enhance treatment adherence and patient's satisfaction.

2.2 Methods and analysis

Study design and setting

This is a parallel-assignment, double-blinded, randomised control trial. The outcome assessor and the data analyst will be blinded to the group allocation of participants. PwMS who meet the inclusion criteria and provide written informed consent will be assigned to two treatments, the VGT or the BPT. The trial protocol has been registered on ClinicalTrials.gov.
The protocol of this clinical trial is reported following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.28 A SPIRIT checklist is available as an additional file (online supple- mental additional file 1). Subjects will be recruited from the patients afferent to Outpatient Rehabilitation Clinic at University Hospital of Ferrara. Patients' recruitment started on 1 December 2017, and it is going to finish on 1 October 2022.

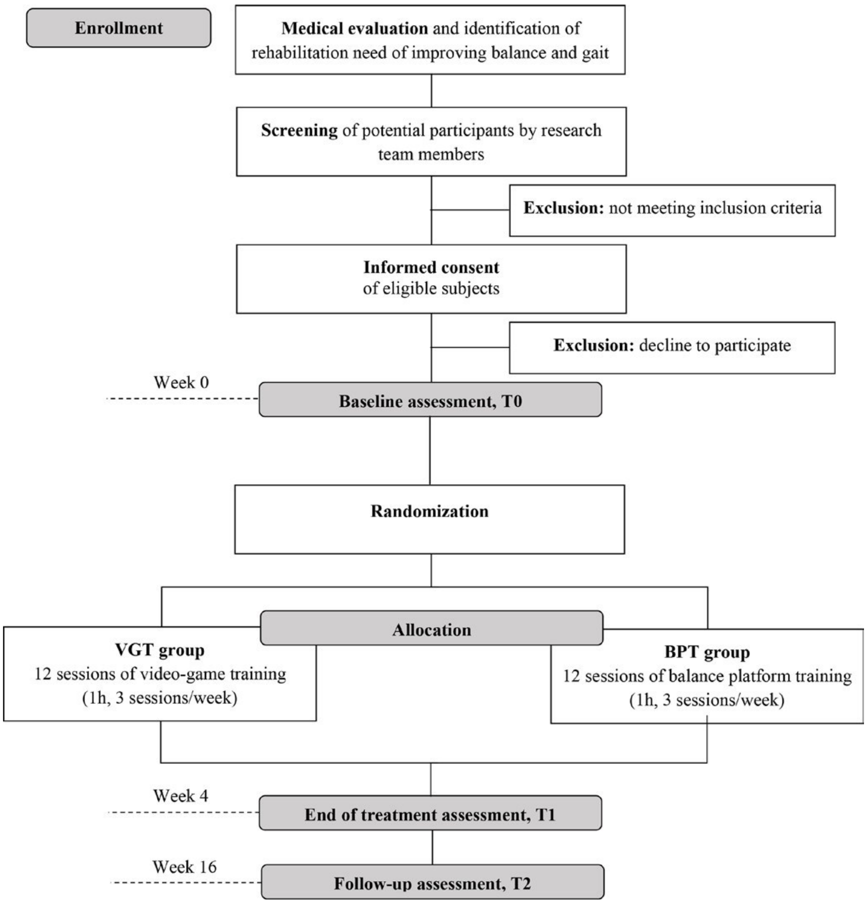
Selection criteria and recruitment of participants

People affected by MS will be included if they meet the following inclusion criteria:

- Men and women, aged 18–60 years;
- Diagnosis of MS (primary or secondary progressive, relapsing–remitting), without relapses in the preceding 3 months;
- Disability rate defined by Expanded Disability Status Scale (EDSS) score from 4 to 5.529;
- Balance impairments with increased fall risk, defined as Timed Up and Go (TUG) >8.4 s30;
- Mini-Mental Status Examination score ≥24/30.31
- Exclusion criteria will be:
- Other (neurological) conditions that may affect motor function;
- Visual impairments (daltonism and visual acuity deficit);
- Medical conditions might interfere with the ability to complete the study protocol safely.

During the first appointment, potential participants will be informed about all the study procedures and screened following the inclusion criteria, suppose they meet inclusion criteria and are interested in taking part in the study. In that case, the physician will give them a letter explaining study purpose and procedures, time commitments, risks, potential benefits, treatment alternatives, study staff contact information and the Consent Form. In the following 3 days, the potential participant will be contacted and asked about its decision; if the subject decides to take part in the study, the research staff will give him/her an appointment for the consign to the signed Consent Form and for the baseline outcome measures, conducted by a physiotherapist. If the subject rejects participation in the study, the research staff remains available for further information. The total number of subjects screened for participation and the number of subjects who decline to participate will be recorded, according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (*Figure 1*) (Schulz et al., 2010).

Figure 1. Consolidated Standards of Reporting Trials flow diagram of the study



*BPT, balance platform training; VGT, video game therapy

Randomisation and blinding

People meeting inclusion criteria who decided to participate will be assigned to one of the two treatment groups through a block randomisation approach (1:1 ratio). The randomisation scheme will be set up in permuted blocks of four to ensure a similar number of participants between groups. The randomisation scheme will be generated using the website http://www.randomization.com and managed by an external administrator to the research group to prevent selection bias. The outcome assessor will be blinded about the subject's group allocation. All outcome data and assignment groups will be organised in different data sets to maintain the blinding during data analysis. The privacy of the participants and their medical records will be guaranteed by treating the data according to the Italian Law n. 196/2003, to the 'Safe Harbor Act' (2000/520/CE) and to the 'European Union Data Protection Directive (95/46/EC 24 October 1995)'.

Intervention

All participants will receive twelve 1-hour training sessions over 4 weeks, resulting in a three sessions/week scheme. To manage possible absence lasting one or more treatment sessions, a potential window of 5 weeks will be set to ensure the achievement of all 12 sessions. Subjects who miss a training session will be contacted by phone to determine the absence's reasons and maintain adherence to following treatment sessions. Subjects who miss more than three consecutive treatment sessions will be excluded from the study.
Every training session consists of about 50 min of exercise and about 10 min of mobility and flexibility activity to prevent muscle soreness due to movement. All interventions will be delivered at the Rehabilitation Clinic of the University Hospital of Ferrara.

VGT

VGT will be delivered with a commercial video game console, Kinect for Xbox 360 game system (Microsoft Corporation, Redmond, Washington, USA). Pre-selected games were chosen from 'Kinect Adventures!' and 'Kinect Sports' (Microsoft Game Studios) that encompassed a wide range of motor activities in a standing position. Specifically, balance and mobility-related motor tasks were trained, such as sidestepping, lateral weight shifting, jumping, walking (lateral, forward and backward), and arm goal reaching.

Kinect is a commercial device therefore calibration of the instrument on the individual patient is not provided. The physiotherapy treatment with this device will be set by the physiotherapist basing on clinical observations of the patient's characteristics, preferences and level of functioning.

A list of games will be tested according to the patient's abilities and preferences. In the following sessions, games will be proposed with a randomised practice approach. Progression proceeds over time according to the patients' motor and balance improvements. Each task will consist of 2–5 min of training and a rest period will be given if necessary. During sessions, the patients will be carefully supervised by a physiotherapist who monitored the patient's safety (eg, risk of falls, impulsive reactions). The physiotherapist will also give performance feed- back and those provided by VGT: visual and augmented (knowledge of both results and performance) (Straudi et al., 2017). Despite variability among treatment protocols available in the literature, our treatment dosage in terms of number of sessions and intervention duration is in line with other studies on the efficacy of exergame in people with neuro- logical disorders (Brichetto et al., 2013; Nilsagård et al., 2013; Bonnechère et al., 2016; Cano Porras et al., 2018).

BPT

Balance/rebalancing, postural stability and weight- shifting exercises with and without visual feedback will be administered using a Balance Platform (Biodex Medical Systems, Shirley, New York, USA) that had been previously tested in patients with MS (Eftekharsadat et al., 2015). Each task will be trained for about 2–3 min, followed by a rest period when necessary. During the first session, the tasks will be set to an 'entry-level'. The exercise progression will be adjusted over time according to the patient's capabilities (intermediate and difficult level). BPT offers visual feedback about reaching goals (augmented feedback). The physiotherapist will carefully supervise the patient and monitor his safety, providing additional external feedback during the activities.

Concomitant care and recommendations

All the subjects will be advised to not undertake other physical treatments until the end of the assessment period. Subjects will also be encouraged to not use the video game console at home for leisure to prevent confounding effects. It will be asked to patients to wear the same shoes and orthosis during all the outcome assessment and training sessions.

Intervention fidelity and monitoring of adverse events

All the interventions will be delivered by a physiotherapist with at least 5 years of experience in the treatment of PwMS, properly formed about VGT or BPT. Training sessions features and comments will be tracked in a precompiled form. Any unpredictable adverse events will be recorded in the patient's registry and the electronic study database. Their management will agree with the related hospital policies, with a referral for appropriate medical follow-up.

Outcome assessment and data collection

All the clinical evaluations will be performed at the Ferrara University Hospital by the same blinded assessor at the three time-point evaluations: (T0) baseline, before the first intervention; (T1) end of treatment, after the 12 therapy sessions; (T2) follow-up, 3 months after the end of treatment. Clinical and posturographic assessment will be delivered by a physiotherapist trained adequately about evaluation procedures. A neuropsychologist with years of experience in the assessment and treatment of PwMS will provide cognitive tests. A physician member of the research team will define the patient's EDSS score. A team member will record the general demographic information (age, gender), comorbidities and medical history of every participant. A summary of the study plan is reported in Table 1.

Table 1. Schedule of enrolment, interventions and assessments

	Study period				
	Enrolment	**Allocation**	**Post allocation**		**Close-out**
Time point	T-1		T0	T1	T2
Enrolment					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
Interventions					
Video game therapy			☐		
Balance platform therapy Assessments			☐		
Primary outcome					
Timed Up and Go test Secondary outcome			X	X	X
Clinical measures and questionnaires			X	X	X
Cognitive and psychological assessment			X	X	X
Posturographic assessment			X	X	X

Primary outcome: functional mobility

This function will be assessed by the TUG test, a reliable and valid performance-based measure of functional mobility (Kalron et al., 2017).The patient will be instructed to stand up from a chair, walk for 3 m, cross a line marked on the floor, turn around, walk back and sit down. The time used to complete the task is recorded using a chronometer. During the assessment, the subject can use any necessary gait aid (not physical assistance). This test will be the first performed during the assessment session to reduce variability due to the subject's fatigue. The TUG test will be repeated three times, and the mean value will be recorded.

Secondary outcome measures

Secondary outcomes will include: (1) clinical measures and questionnaires, (2) cognitive and psychological assessment and (3) posturographic assessment. All secondary outcome measures will be carried out in random order.

Clinical measures and questionnaires

- Dynamic Gait Index (DGI): gait, balance and risk of fall are measured using DGI. DGI will evaluate not only usual steady-state walking but also during a more challenging task (ie, cross obstacles, slalom). The subject will perform eight functional walking tests and score out of three (maximum total score is 24) (Mañago et al., 2020).
- Four Square Step Test (FSST): this timed test is intended to challenge the rapid change in direction while stepping forward, backward and sideways over a low obstacle. The faster the time measured to perform the task signifies a superior level of dynamic balance abilities. The minimal detectable change estimate for the FSST in MS is 4.6 s, and it was found to be a valid assessment tool in MS (Moore et al., 2017).
- Functional Reach Test (FRT): this test assesses the subject's stability by measuring the maximum distance an individual can reach forward while standing in a fixed position. A

longer reaching distance indicates better postural control (Soke et al., 2021).

- Multiple Sclerosis Impact Scale—29 (MSIS-29): this health-rated quality of life questionnaire assesses the impact of MS on physical and psychological functions. It is formed by 29 items on ADL I and II: 20 about physical activity and 9 about psychological status. Each item can be scored with a value from 0 to 5; the total score is given by the sum of all the items and then is transformed in a range from 0 to 100 (Hobart et al., 2001).
- Multiple Sclerosis Walking Scale—12 (MSWS-12): this questionnaire assesses the impact of MS on walking ability. It is formed by 12 items, asking the patient about his perception on gait speed, running, confidence ascending/descending stairs, balance and fatigue. The total score is obtained by the sum of the score of each item (0–5) and then transformed into a value from 0 to 100 (Marengo et al., 2019).
- Modified Fatigue Impact Scale (MFIS): this 21-item questionnaire assesses the perceived impact of fatigue on the subscale physical, cognitive and psychological functioning during the past 4 weeks. MFIS has been recommended for use by the Multiple Sclerosis Council for Clinical Practice Guidelines (Rooney et al., 2019; Coghe et al., 2018).

Cognitive and psychological assessment

- Beck Depression Inventory-Second Edition (BDI- II): this is a 21-item self-report measure that quantifies the severity of depression and over behavioural characteristics of depression (Sacco et al., 2016).
- State Trait Anxiety Inventory (STAI-Y): this self-report questionnaire measures the presence and severity of current symptoms of anxiety and a generalised propensity to be anxious. There are two subscales: 20 items allocated to each of the State Anxiety (S- Anxiety) and Trait Anxiety (T-Anxiety) (Santangelo et al., 2016).
- Test of Attentional Performance (T.A.P. V.2.3): attentional performance will be evaluated using a neuropsychological computer test. Errors, omissions and reaction times will be recorded as outcomes of performance. Three modules of the T.A.P. will be administered: Go-No Go subtest as it allows assessment of the specific ability of subjects to suppress undesired responses; alertness subtest that measures the simple reaction time in response to a visual stim- ulus and, divided attention subtest, that explored with 'dual-task' test the ability to attend simultaneously two stimuli (visual and acoustic) processed in parallel (Zimmermann & Fimm, 2002).
- Stroop Color-Word Test (SCWT): this neuropsychological test is used to assess the ability to inhibit cognitive interference when processing a specific stimulus feature impedes the simultaneous processing of a second stimulus attribute. Subjects are required to read three different tables as fast as possible. Two of them represent the 'congruous condition', in which participants are required to read names of colours printed in black ink and name different colour patches. Conversely, the third table represents the incongruent condition, in which participants are required to name the colour of the ink instead of reading the word (Coghe et al., 2018).
- Symbol Digit Modalities Test (SDMT): this neuropsychological test quantifies cognitive processing speed. It consists of orally report the correct number corresponding to a symbol in a pseudorandom sequence of nine symbols as quickly as possible (Benedict et al., 2017).

Posturographic assessment

Instrumented basic balance evaluation: Force platform measurements are routinely used as objective markers of subjects' balance ability (Sun et al., 2018; Severini et al., 2017). Several parameters can be extracted from the force platforms that correlate with balance ability and risk of falls in PwMS. During the instrumented tasks, subjects will be asked to stand on a force plate (BERTEC Model 4080–10, Bertec, Columbus, Ohio, USA) with arms parallel to their body. Each subject will undergo five repetitions (each lasting 60 s) of two tasks that will consist in standing with the eyes open and standing with the eyes closed. The movements of the centre of pressure (CoP) of the subjects will be recorded. A series of features will be extracted from the CoP traces to inform on different balance characteristics of each patient and the specific effect of each of the proposed therapies. Features that will be analysed include different measures of CoP displacement in the anteroposterior (AP) and

mediolateral (ML) directions, the CoP path length (total, AP and ML) and the CoP average and maximum speed (Straudi et al., 2017).
Dual-tasking assessment will be performed combining posturographic and neuropsychological tests: subjects will be asked to complete SCWT standing on the force plat- form, ensuring a similar condition to single-task SCWT. Head position will be fixed using a large panel fixed on the wall facing the force plate in order to prevent subjects lowering their head and distort the data. The ability to inhibit cognitive interferences during quiet and standing conditions will be compared.

Data management

Data analysis will be performed according to the research hypothesis mentioned. Stata Statistical Software (Release 13.1.: StataCorp LP) will be used for data analysis.

Sample size and power

The primary outcome of this study is to highlight differences in the time used to perform the TUG test between PwMS who underwent VGT and BPT. Our preliminary results from an unpublished pilot study (n=6) shown a VGT effect size of 0.93 in people with MS and EDSS <6. Given equal allocation between treatment and control arms, and using 80% power and alpha of 5%, we would need 40 subjects to complete the study. Conservatively, we expect a 10% rate of drop-out. Thus the sample size will be increased by 10% to 48 subjects (24 per arm).

Statistical analyses

Descriptive statistics (mean and 95% CI) will be reported before treatment, after treatment and at 3 months follow-up for all the selected variables (clinical, instrumental and questionnaires). Specifically, TUG changes after treatments will be considered as our primary endpoint, whereas changes of all the other outcome measures (DGI, FSST, FRT, MSIS-29, MSWS-12, MFIS, BDI-II, STAI-Y, SCWT, SDMT, T.A.P., posturographic variables) will be treated as secondary endpoints. Between- group differences will be explored with the Wilcoxon rank-sum test. Moreover, a repeated-measures analysis of variance (within-group factor: TIME; between-group factor: TREATMENT) will be conducted to detect the main effects for treatment and time for all the available outcomes. To calculate the effect size of both treatments, we will use Cohen's d (Cohen, 1988). Results will be reported as mean and 95% CI. Significance will be recognised for p<0.05.

Intention-to-treat

Every attempt will be made to avoid missing data through a careful check of self-reported measures, as self-administered questionnaires. An intention-to-treat analysis was carried out on all outcome measures. Missing data will be treated using the last observation carried forward approach.

Data monitoring and interim analysis

The trial does not include Data Monitoring Committee. An update on trial progress will be shared with Ferrara University Hospital Research office every 6 months. The research coordinator will be responsible for interim analysis to determine if the trial should stop, modify or carry out. The research group will discuss any subsequent modifications and communicate to the funding agency and Ethics Committee.

Patient and public involvement

The research question in this study starts from years of experience in rehabilitation of PwMS and previous research study on the use of VGT in balance impairment. The drafting of the study was submitted to the Multiple Sclerosis Italian Society (FISM) and reviewed to better meet patients' needs. The final version of the study reflects the collaboration between the research group and the patients' association.

Ethics and dissemination

The Ethics Committee of Ferrara approved this study with approval number 170 691 on 19 October 2017. Communication of results and conclusions will be assigned to high-quality journals and national and inter- national conferences. Results will also be disseminated through FISM annual conference. People with MS will be informed about the possible efficacy of the proposed treatment through MS support groups.

2.3 Discussion

This trial may highlight the role of gaming in the rehabilitation of PwMS, enforcing the utilisation of new technologies in daily clinical practice among subjects with mild-to-moderate disability (Dalmazane et al., 2021).

Our expectation from the proposed research is to observe a more significant effect on mobility, balance and dual-tasking through virtual reality training compared with a conventional approach. A meta-analysis by Casuso-Holgado et al. (2018) found that active video game training could be considered as effective as conventional training in improving balance and gait abilities in PwMS, but treatment modalities' variability among the included studies may give rise to various interpretations. Furthermore, we expect different results due to the dosage of our treatment compared with those of included studies in the review and treatment administration modalities that include home-based interventions and one intervention based on telerehabilitation. Instead, our expected results are in line with what was found by Nascimento et al. (2021) in their systematic review regarding fatigue, quality of life and balance. Making the rehabilitative session more engaging for patients may increase involvement and adherence in the rehabilitation process. Increased participation and motivation were already being observed in PwMS treated with gamified training (Sokolov et al., 2018; Dalmazane et al., 2021). Traditional rehabilitation approaches is often repetitive and boring, decreasing patient's interest and exercise participation. However, patients' satisfaction represents one of the key features for treatment adherence and rehabilitation success, particularly in PwMS (Jeong et al., 2019). Virtual reality-based therapy has been proposed to overcome the drawbacks of conventional rehabilitation, providing augmented feedback during training that contribute to a more effective motor learning (Meca-Lallana et al., 2020). Active video games may offer an enriched environment useful for subjects with neuropsychological disorders, like attentional deficit or impaired alertness. Exergaming has recently been studied as an effective strategy to improve dual-task performance in people with neurological disabilities (Mura et al., 2018). Indeed, active video games not only engage patients in motor activities, but it simultaneously require subjects to use cognitive abilities for managing inputs into an enriched environment (Prosperini et al., 2013). Therefore, we expect to observe greater modifications on cognitive and psychological evaluation of people who received rehabilitation through video game plat- forms. Recently, gaming consoles introduced in clinical and research settings may represent a low-cost opportunity of delivering virtual-reality training. For this reason, the use of VGT may be delivered at home, promoting self- management strategies to improve mobility function and long-term outcomes. Our study may have several limitations. First, the absence of evaluation over 3 months could not give any information about the long-term effects of active video game training. Second, we will not use any instrument to assess patients' satisfaction with the experimental treatment. Third, any neuroimaging technique will be used to show the possible neuroplastic changes in the brain due to VGT. Finally, we will not study the effects of combined treatment of VGT and other rehabilitative techniques for balance and mobility, despite combining treatments seems to augment training efficacy and boost effects of a single approach (Maggio et al., 2019). Further studies should consider these possible limitations and confirm the results related to physical and neuropsychological outcomes.

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ACTION OBSERVATION TRAINING FOR UPPER LIMB STROKE REHABILITATION: THE ROLE OF ATTENTION AND ENGAGEMENT

ABSTRACT

Purpose: The restoration of motor function is essential in daily life in stroke patients. Although patient's engagement and attention can affect motor recovery, in most rehabilitation interventions are not considered. This study aims to evaluate the effects of an Action Observation Training (AOT) on attention and patients' engagement and their influence on motor recovery.

Method: Twelve subacute stroke patients (mean age 57.9, 70% males) participated in the study; all underwent AOT 5 days a week, for a total of 4 weeks. They were divided into two subgroups: with/without attention deficit based on the neuropsychological evaluation. The accuracy of interactive computerized exercises was used as a measure of concentration during the training. A questionnaire was used to measure patients' engagement.

Results: The overall adherence to the training was high; no participant dropped out. Regarding the accuracy, the trend showed a sustained improvement up to the third week and then decayed. Moreover, the group with attention deficit reported a lower level of engagement and a lower mean accuracy; considering the accuracy for each week of AOT, the difference between the two subgroups emerges in week 3 and week 4. Mean engagement score was a potential predictor to mean accuracy score, and the presence of attention deficit was a potential predictor of engagement. All patients improved motor function; however, the group without attention deficit reported a more significant gain.

Conclusions: Attentional deficits could play a critical role in upper limb motor recovery. Our results suggest that AOT improved attention over the first three weeks of training and that individuals with attentional deficits presented a lower engagement during the training and poorer motor outcomes.

Keywords: stroke, attention, engagement, motor recovery, Action Observation Training

Highlights

- Attentional deficits and motor dysfunction are frequent in stroke patients
- Patient engagement and attention play a crucial role in motor recovery
- Action observation training improve motor and attentional abilities

3.1 Introduction

Stroke is one of the leading causes of adult disability with 75% of patients suffer from upper extremity dysfunction and 50% experience cognitive dysfunctions (Serrano et al., 2007; Huang & Yang, 2014; Sebastián-Romagosa, 2020), which impact their quality of life and return to work (Hochstenbach et al., 2001). These are two critical factors that influence activities of daily living. Additionally, there are numerous psychiatric disorders that may occur after a stroke. Among these, depression and anxiety are the most common disorders that can occur as comorbid conditions and produce a significant degree of psychological distress and influence quality of life; furthermore, these disorders have been shown to inhibit physical recovery from stroke (Chemerinski et al., 2000).

Several studies demonstrate that stroke patients improve over time in their level of overall disability and day-to-day cognitive functioning (Hendricks et al., 2002; Hyndman et al., 2008; Barker-Collo et al., 2010).

Among cognitive deficits, attention deficits are most typical in stroke patients. Roughly 46—92% of stroke survivors presented attention deficits early after a stroke that improved over six weeks (Robertson et al., 1997; Stapleton et al., 2001; Hyndman & Ashburn; 2003; Hyndman et al., 2008).

Attentional impairments occur in a wide variety of deficits, such as diminished concentration, distractibility, reduced error control, reduced multitasking capabilities, mental slowness, and mental fatigability (Loetscher et al., 2019).

Hyndman et al. (2008) suggested a plausible causal relationship between attention deficits and poor functional recovery, showing that sustained, divided and selective attention deficits at discharge correlated with mobility, balance and ADL outcomes 12 months later. Perhaps, attention is a prerequisite for learning, and that incapacity to attend hamper re-learning of movements, thus impede recovery.

Stroke rehabilitation seems to be most efficacious when therapists encourage patients' active participation and engagement (Pyoria et al., 2007; Lequerica et al., 2009) that appears to be determined by their emotional state and level of cognitive functioning (Lequerica et al., 2009; Bright et al., 2015).

From a neuropsychological point of view, a raised patient's engagement seems related to greater attention during exercise (Danzl et al., 2012). Several studies showed that positive clinical outcomes (i.e. reduced depression and better cognitive and motor outcome) correlate with the effective recruitment of attention (Lequerica et al., 2006; Lequerica et al., 2009; Brett et al., 2017).

The debate concerning the influence of the side of lesion on attention and recovery remains contentious: attention is recognized to be mainly a right hemisphere and frontal lobe function (Pardo et al., 1991; Lewin et al., 1996; Robertson et al., 1997) but others argue that side of the lesion is not essential (Hyndman & Ashburn, 2003; Hyndman et al., 2006).

Recently, new rehabilitation strategies have been proposed to increase upper limb recovery after stroke, including Action Observation Training (AOT), a mirror neuron system (MNS)-based training which commonly includes action observation and action execution of goal-directed daily actions (Sarasso et al. 2015; Zhang et al., 2018). It induces specific motor facilitation in the corticospinal system that increases the excitability of the injured sensorimotor system in the primary motor cortex facilitating the reorganization of the brain in patients by activating central representations of actions through the mirror neuron system (Celnik et al., 2008; Wang et al., 2010). Directing visual attention explicitly during action observation training facilitates corticospinal excitability and may quicken motor re-learning through observation (D'Innocenzo et al., 2017).

This pilot study aims to investigate the role of attention and patient's engagement on motor recovery after a four-week Action Observation Training program in subacute stroke patients.

3.2 Methods

Subacute stroke patients were recruited at Ferrara University Hospital. Subjects were evaluated and interviewed by a trained physiotherapist and psychologist before being included in the study and were assessed to determine the presence of inclusion/exclusion criteria.

All participants met the following inclusion criteria: 1) males and females aged 18 years or older; 2) diagnosis of first cerebral stroke (ischemic or haemorrhagic) verified by brain imaging within eight weeks; 3) upper limb motor function defined by an FMA-UE score < 55.

The exclusion criteria included: 1) any additional medical condition that would affect the ability to comply with the study protocol; 2) any severe visual and language impairment; 3) contraindications to single-pulse TMS (i.e. presence of intracranial metal implants, positive history of epilepsy, frequent neck pain or migraines, implantable devices) and 4) pregnancy.

The Ferrara Ethics Committee approved the study protocol. The trial protocol was registered to ClinicalTrials.gov, with the number NCT04622189.

The objectives, procedures, timelines, risks and potential benefits of the study and its requirements were explained to all participants before conducting the study. All participants signed a written informed consent form. The trial protocol has been registered on ClinicalTrials.gov (NCT04622189). All procedures were performed according to the ethical standards of the Declaration of Helsinki. This study was a prospective open clinical trial.

At baseline, a single-pulse transcranial magnetic stimulation (Single-pulse TMS) was used to study the excitability of the cortico-spinal tract (MEPs, Motor Evoked Potentials) of the primary motor cortex (M1), and a neuropsychological assessment were performed.

The neuropsychological assessment included the Cognitive Reserve Index questionnaire (CRIq) and the Test of Attentional Performance (TAP, Version 2.3.1). The first is used to evaluate an individual's cognitive reserve through the compilation of information relating to their entire adult life. The questionnaire includes 20 items grouped into three sections witch returns a subscore: education, working activity, and leisure time (Nucci et al., 2012). TAP is a standardized computer-based assessment of various aspects of attention that is widely used as a diagnostics tool (Zimmermann & Fimm, 2002). For the present study, two subtests of the TAP were selected, which correspond with the subtest of the divided attention and Go/NoGo. The first, assess the ability to pay attention simultaneously ongoing processes; in this test, a visual and an auditory task must be processed in parallel. The second, assess the ability to perform an appropriate reaction under time pressure and simultaneously inhibit an inappropriate behavioural response. Test form "2 of 5" (2 critical stimuli amongst five stimuli) is used; it consists of a sequence of five squares with different patterns appearing on the screen. Two of these squares are defined as target stimuli.

All subjects underwent Action Observation Training (AOT) for four consecutive weeks, five days per week. Each session consisted of 3 blocks (sessions) per day of about 15 minutes each for a total of 45 min per day. To measure the attentional level index during the four weeks of training, we used the accuracy of interactive computerized exercises. Finally, an engagement questionnaire was used to identify the level of involvement of the treatment. The AOT engagement questionnaire is an 8-item, self-reported scale. It was developed to measure engagement with physical and functional rehabilitation intervention. It includes three categories of items: the satisfaction of the treatment, perception of mental fatigue, level of motivation.

The Fugl-Meyer Assessment for Upper Extremity (FMA-UE) was used as the primary motor outcome measure; it was used to assess the degree of sensorimotor arm impairment. This scale is considered the most sensitive to therapeutic change early after stroke in patients with arm paresis (Fugl-Meyer et al., 1975; Platz et al., 2005; Sullivan et al., 2011). The Box and Block Test (BBT), to assess manual dexterity (Hsiao et al., 2013), and the Barthel Index (BI), an ordinal scale to measure the degree of assistance required by an individual of mobility and self-care activities of daily living (Mercuri et al., 2019) were also performed.

Action Observation Training (AOT)

Participants sit with their arms resting on the table, at a distance of 65 cm from a 24-inches LCD screen on which the stimuli were presented. Each AOT session was composed by ten different videos repeated four times (40 videos per block); in this way, patients observed 120 videos per day. The videos were randomized over the four weeks of treatment, and the order in which they were presented was kept fixed for all subjects.

The video movements were displayed from a first-person perspective to maximize corticomotor excitability. The movements in the video were performed by a single non-disabled women actor wearing gloves. The following common categories of actions were included in this study: (a) transitive gestures (i.e. actions performed during spare time, in the office or while cooking to more simple and general reaching to grasp or pinching) (b) intransitive gestures. The actions have been shown with the right or left hand depending on the patient's hemiparetic side. Patients were asked to carefully observe the upper limb movement video clips to prepare themselves to imitate the presented actions as accurately as possible. In each block, the following elements were presented in sequence: (1) a fixation period with a countdown (duration: 3000 ms); (2) start of the video clip with a static image of hands before starting movement (duration: 1000 ms) (3) start of movement (duration: variable depending on the video between 4000 and 6000 ms). At the end of video 4, which was repeated as the 16th, 23rd and 38th stimulus, each subject was asked to imitate the movement. To maintain concentration in the activities and, thus, maintain an adequate performance level in the treatment, interactive computerized exercises were created.

These include additional questions that request sensorimotor processing, i.e. they are characterized by simultaneously requiring sensory (auditory/visual) and motor processing (imagine or active movement). The questions included choice-making, spot-the-difference, order and sequencing, series completion, identifying the movement and its meaning, which required attentional and other cognitive skills (as working memory and executive functions). The total number of questions is 120 (2 questions per session). Participants received online feedback for each question.

For the entire duration of the treatment, the therapist has provided verbal instructions and help when needed.

Data analysis

Statistical analysis was performed with the Jamovi Computer Software (Version 1.6) (*Jamovi*, Sydney, Australia). Baseline clinical and demographical characteristics were expressed as mean and standard deviation or percentage depending on variables distribution. Regarding attentional performance (TAP), all reaction time data are given as mean and standard deviation of raw scores. Based on a clinical evaluation our sample was categorized in two classes: attention deficit (AD) or not (No_AD) and between-group differences were explored with the Independent t-test. To investigate time effects (T0 and T1) the Paired-sample t test was applied separately for AD and No_AD subgroups; results were reported as mean and 95% CI. For patient's engagement questionnaire, the answers were expressed as a mean for each question for each subgroup. The accuracy of attentional questions were calculated separately during the four weeks of training as mean and standard deviation. A repeated-measures analysis of variance (RM-ANOVA) ($p < 0.05$) with time (4 levels: W1, W2, W3, W4) as within-subject factors and attention deficit (2 levels: Presence, Absence) as between-subject factor was performed to reveal the difference in total accuracy within each group through the four weeks of treatment. For this analysis, in case of significant main effects and/or interactions, Bonferroni-corrected post hoc tests were computed and, in case of violation of the sphericity assumption at Mauchly's test, Greenhouse-Geisser correction was applied to the degrees of freedom. Correlations between clinical and demographic variables were tested with the Spearman-Rho test. Moreover, a linear regression analysis was performed, including those variables that correlated significantly with the FMA total increment (dependent variable) and a linear regression model was used to underline variables that predicted the patient's engagement and mean accuracy (dependent variables). Statistical significance was set at a level of $p< 0.05$.

3.3 Results

A total of twelve subacute stroke patients with arm paresis were recruited. Two patients were excluded because they did not complete the treatment for reasons related to the COVID-19 pandemic. Ten patients (median age 57.9, 70% males, 27.1 days of stroke onset) concluded the AOT protocols. Patients were divided into two subgroups: subjects with attention deficit (AD) (n=6) and subjects without attention deficit (No_AD) (n=4). Both subgroups showed homogeneous demographic and clinical motor characteristics at baseline, except for the dominance of the hand, for which the group No_AD had a majority of left-handed people (75% of patients). See Table 1a. Whereas, the two subgroups showed a statistically significant difference for the neurocognitive and psychological variables at baseline. The AD group had the neglect syndrome and the lowest cognitive reserve index. They also showed anxious and depressive signs/symptoms and longer reaction times in the Go/Nogo and dual tasks. See Table 1b.

Table 1a. Demographic and clinical physical data of the sample at baseline

	Total sample (N=10)	No_AD group (N=4)	AD group (N=6)	*P value*
Stroke severity (mild,%)	5 (50%)	3 (75%)	2 (33.33%)	0.242
Sex (male,%)	7 (70%)	3 (75%)	4 (66.66%)	0.807
Age (mean, SD)	57.9 (9.22)	56.5 (4.20)	58.8 (11.8)	0.719
Stroke type (hemorrhagic, %)	6 (60%)	3 (75%)	3 (50%)	0.486
Dominant hand (left, %)	3 (30%)	3 (75%)	0 (0%)	0.005*
MEPs (positive, %)	8 (80%)	4 (100%)	4 (66.66%)	0.242
NIHSS entry (mean, SD)	12.6 (3.24)	10.3 (2.89)	13.7 (3.01)	0.157
BBS discharge (mean, SD)	43.4 (12.8)	53.0 (3.46)	37.0 (12.8)	0.043*
RCS-E entry (mean, SD)	11.5 (1.43)	10.8 (1.50)	12.0 (1.26)	0.192
FIM entry (mean, SD)	59.7 (7.70)	65.0 (6.08)	57.0 (7.38)	0.152
MI - Upper Limb entry (mean, SD)	34.4 (32.5)	48.8 (23.0)	23.0 (20.2)	0.263
TCT entry (mean, SD)	68.9 (19.1)	74.5 (0.707)	66.6 (23.0)	0.665

Abbreviation: Motor evoked potentials (MEPs); National Institutes of Health Stroke Scale (NIHSS); Berg Balance Scale (BBS), Rehabilitation Complexity Scale – Extended (RCS-E); Functional Independence Measure (FIM); Motricity Index (MI), Trunk Control Test (TCT). *p<0.05

Table 1b. Neuropsychological and psychological clinical data of the sample at baseline

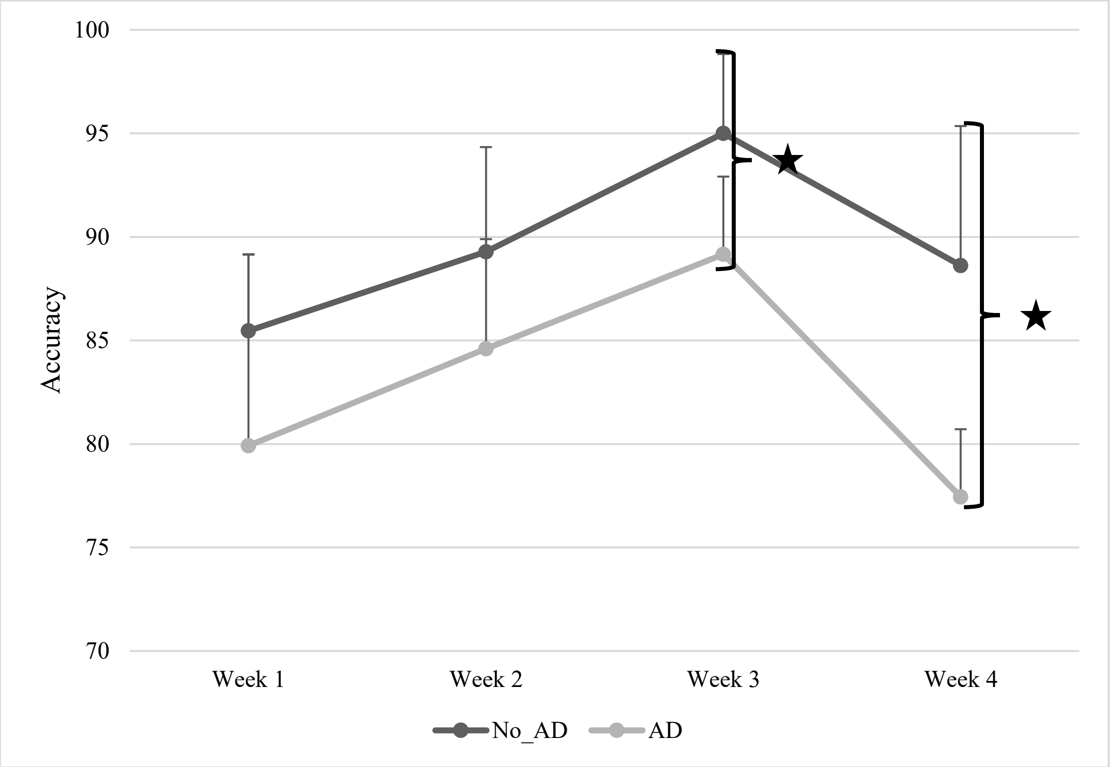
	Total sample (N=10)	No_AD group (N=4)	AD group (N=6)	*P value*
Go/Nogo_Reaction Time (mean, SD)	591 (130)	444.069 (40.569)	678.949 (52.368)	<0.001*
Dual task_Reaction Time (mean, SD)	815 (185)	667.644 (20.742)	925.634 (173.980)	0.051
Anxious and depressive signs/symptoms (n,%)	4 (40%)	0 (0%)	4 (66.66%)	0.035*
Neglect(n,%)	4 (40%)	0 (0%)	4 (66.66%)	0.035*
CRIq (mean, SD)	105 (17.5)	120 (14.9)	92.2 (4.087)	0.005*
CRI-Education (mean, SD)	96.2 (14.9)	108 (16.3)	87.200 (3.834)	0.029*
CRI-Working Activity (mean, SD)	102 (12.1)	111 (13.1)	94.8 (4.438)	0.037*
CRI-Leisure Time (mean, SD)	112 (16.7)	126 (12.8)	100.4 (7.829)	0.007*

Abbreviation: Cognitive Reserve Index questionnaire (CRI-q). *p<0.05

The trend of the accuracy of the questions during the four weeks is shown in Figure 1; both groups show sustained improvement up to the third week and then decays.

The difference between the two subgroups in the total accuracy of the four weeks is statistically significant (p=.036): the No_AD group shows a higher percentage of accuracy (mean 89.6 ± 2.27 %) than the AD group (mean 82.8 ± 5.00 %). Considering the accuracy for each week of treatment, the difference between the two subgroups emerges in week 3 (No_AD: mean 95.0 ± 3.83 %; AD: mean 89.2 ± 3.75 %; p= .044) and week 4 (No_AD: mean 88.6 ± 6.74%; AD: mean 77.4 ± 3.26%; p= .007).

Figure 1. Accuracy interactive computerized exercises during the four weeks of AOT



Abbreviation: No_Attention Deficit (No_AD); Attention Deficit (AD).
Description: Data are reported as mean and standard deviation for each week. Stars indicate p < 0.05.

The RM-ANOVA comparison showed a significant main effect of TIME of total sample (F(3, 27)= 11.3, p<.001, ηp^2=203.5); Bonferroni-corrected post hoc tests confirmed an overall accuracy's difference specifically between week 1-week 2 (p=.036), week 1-week 3 (p=.004), week 3-week 4 (p<.001). A second RM-ANOVA showed a significant effects between groups (F(1,8)= 6.34, p= .036, ηp^2 =444.8); post hoc pairwise comparison confirmed the effects of attention deficit on accuracy (p=.036). *Post hoc* tests for the interaction confirmed a significant accuracy difference between week three and week four within the same subgroups (AD p=.004; No_AD p=.006).

The physical clinical results (difference between a final score and initial score) were reported separately for the two subgroups (AD and No_AD).
All patients showed an increment in motor and functional outcome measures; however, the No_AD subgroup reported a more significant increment. However, all clinical measures for either group were not significant, except for FMA-UL (p=.013). Results were reported in Table 2.

Table 2. Median (± SD) and significance of rehabilitative gain after AOT

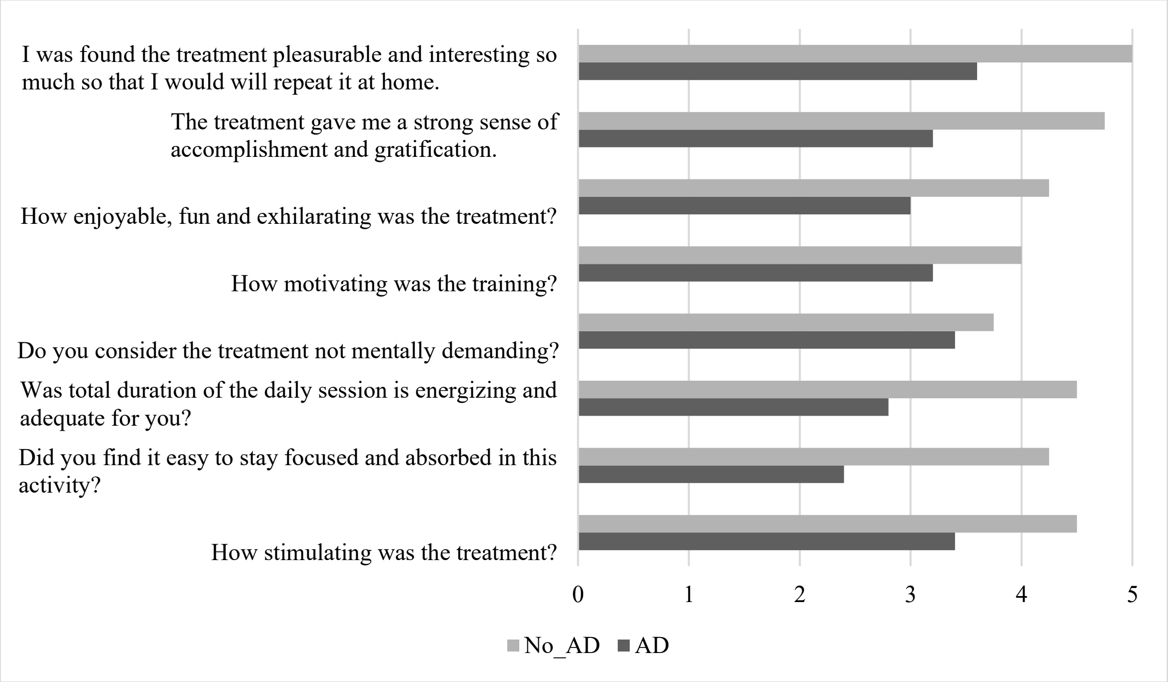
	Total sample (N=10)	No_AD group (N=4)	AD group (N=6)	*P value*
Δ FMA-UPPER LIMB	6.521 (4.680)	10.8 (5.68)	3.33 (1.21)	0.013*
Δ FMA-WRIST	2.747 (3.178)	4.25 (3.10)	1.33 (3.33)	0.201
Δ FMA-HAND	3.811 (4.398)	5.75 (6.29)	1.83 (3.06)	0.219
Δ FMA total	13.534 (11.772)	21.0 (16.4)	7.33 (6.25)	0.096
Δ BBT – PARETIC LIMB	11.338 (12.500)	13.8 (12.0)	8.00 (15.0)	0.540
Δ BI	25.49 (20.99)	38.8 (26.9)	15.8 (16.6)	0.130

Abbreviation: Fugl-Meyer Assessment (FMA); Box and Block Test (BBT); Barthel Index (BI). *p<0.05.

CRI Working activity score was positively associated with an increment of FMA-UL (rho=0.786, p=.048); in the adjusted linear regression model, it remained a significant predictor (p=.005). In the adjusted multiple regression model (F(3)=3.21; R2=.616; p=.048), attention deficit (p=.015), stroke severity (p<.009) and anxious and depressive signs/symptoms (p<.001) remained a significant predictor for increment of FMA total score.

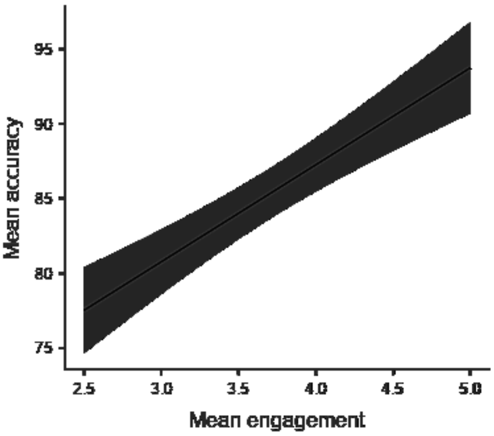
The overall adherence to the training was high; no participant dropped out. The level of engagement was statistically different between the subgroups (p= .013): the NO_AD group reported a higher level of engagement (mean 4.375) than the group with a deficit (mean 3.125). The AD group described the AO training as less motivating and stimulating and perceived a minor sense of accomplishment and gratification. They reported significant difficulties in focused in the training; they defined it a more claiming mentally demanding task, and described the duration of the daily session as less adequate. Finally, they perceived the training as less fun, energising, and less pleasure and enjoyable to repeat it at home. See Figure 2.

Figure 2. AOT engagement questionnaire

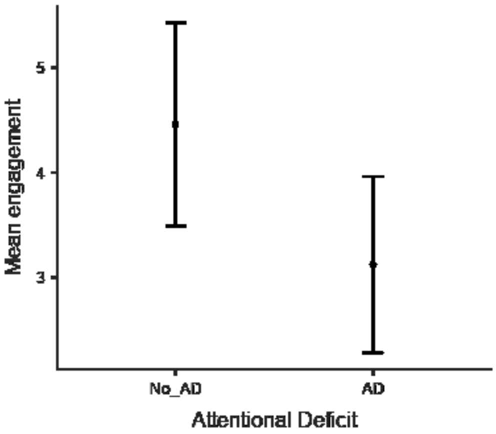


The mean engagement score was positively associated with the mean accuracy score (rho=0.966, p<.001) and negatively associated with attention deficit (rho=- 0.873, p=.002). In the adjusted linear regression model, the mean engagement score (p<.001) remained a significant predictor to mean accuracy score, and in a logistic regression model, the presence of attention deficit (p=.044) was a significant predictor to the engagement score. See Figure 3.

Figure 3. Linear regression analysis



Description: Overall correlation between mean engagement and mean accuracy.



Abbreviation: No_Attention Deficit (No_AD); Attention Deficit (AD).
Description: Mean and standard deviation of engagement in the two groups (No_AD and AD).

3.4 Discussion

Simultaneously, stroke survivors may suffer from motor, cognitive, and psychological deficits, with mutual implications for the rehabilitation program and quality of life.

Motor impairments as hemiparesis, coordination problems, and spasticity are usual and affect patients' autonomy, with a high variability of recovery (Schaechter, 2004). Motor and cognitive impairments are often managed as distinct entities, and there is little evidence regarding how they are related. Attention is the main post-stroke cognitive deficit, and it is being prevalent after right hemisphere lesion (Tuhrim, 1993). Even if our sample was small, 60% of patients with injury in the right hemisphere show attentive deficits. Attention deficits are stated with a mutable incidence ranging from 46% to 92% and may interest various aspects of the attention process (Barker-Collo 2009; Hyndman et al., 2008). The group of patients with attention deficit shows a poor performance with longer reaction times both to the Go / No-go test and dual-task of the TAP. Thus, a comprehensive assessment is required to determine early what forms of attention deficit are present and their cognitive rehabilitation. Moreover, as in our sample, attention deficits overlap with other neuropsychological deficits, particularly neglect; these patients generally show a decrease in vigilance over time (Malhotra et al., 2009), a deficit in sustained attention (Hjaltason et al., 1996; Robertson et al., 1997), low general arousal (Heilman et al., 1978) with deficits in phasic alertness (Husain et al., 1997). Assessment of cognition and attention should be a recommendable focus in stroke rehabilitation (Duncan et al., 2005). These disorders have a notable impact on everyday functioning and constitute an obstacle to successful rehabilitation (Hyndman et al., 2008, Hyndman & Ashburn, 2003). Engaging in educational and working pursuits and leisure activities (e.g., physical, cognitive and social activities) is commonly considered to give the brain a "cognitive reserve" that can be drawn upon when needed (Stern et al., 2012). Indeed, in our study, the group of patients with attention deficit shows a lower cognitive reserve index in all areas: education, work and leisure. Specifically, the "working activity" subsection of CRIq is positively associated with the increment of FMA-UL. Thus, it may be considered a potential predictor of stroke recovery. A cross-sectional study showed that those with higher cognitive reserve had significantly less cognitive deficits and functional disability in the acute post-stroke setting (Umarova et al., 2019). Analogously, longitudinal studies reported that cognitive reserve preserves memory and global cognition, reducing the development of post-stroke dementia independently of socioeconomic status (Ojala-Oksala et al., 2012; Booth et al., 2013).

Stroke has a meaningful impact on psychological wellbeing. Typically, stroke survivors suffer from sleep disturbances, concerns about their future due to disabilities, low motivation and low self-esteem (Hart et al., 2003). This psychological distress can lead to psychiatric problems: prevalence of moderate to severe anxiety and depression were found to be 21.1% and 22.8%, respectively (Barker-Collo, 2007). In the neurocognitive area, depression and anxiety symptoms can affect executive function, memory, speed, and motor processing (Verdelho et al., 2013). A systematic review and meta-analysis reported a significant association between less education and increased risk of post-stroke depressive symptoms, even though with significant heterogeneity (Backhouse et al., 2018). Cognitive impairment constitutes a substantial worldwide health burden that also affects psychological wellbeing (Cumming et al., 2013). In our study, patients with attention deficit show a higher percentage of anxiety and depression. Psychiatric problems may delay the recovery process and impair cognitive functioning due to adaptations to unhealthful lifestyles or non-compliance to rehabilitation (Rasquin et al., 2005). In our study, stroke severity, the presence of anxious and depressive symptoms, and attention deficits were all predictors of motor recovery after AOT. The treatment led to an improvement in all patients without a statistically significant difference, except for proximal upper limb functioning, in which the treatment shows a significant difference in favour of group without attention deficit. Thus, cognitive impairment, influencing motor recovery and ability in ADL, is considered a priority in stroke rehabilitation (Bernhardt et al., 2019); indirectly, cognitive impairment reduces participation and adherence to rehabilitation (Cumming et al., 2013).

The cognitive system supports motor execution in terms of planning the computational steps and of attention on internal and external sensorimotor feedbacks to monitor and regulate the performance (Peters et al., 2015; Goldberg & Segraves, 1987; Proto et al., 2009). Cognitive functions have a crucial role during motor and functional rehabilitation programs; indeed, high attention and memory may allow people to engage better with the proposed tasks (Loetscher et al., 2019). Physical performance six months after stroke onset was related to cognitive impairment on admission and cognitive improvement over six months (Saxena et al., 2007). Deficit on selective attention and distractibility are reportedly ordinary in acute phase stroke patients and are associated with functional impairment (Stampleton et al., 2001); sustained attention two months after stroke onset predicts functional recovery two years post stroke (Robertson et al., 1997). In a study by D'Imperio et al. (2021), pre-treatment sensorimotor and attentional abilities were found to influence motor recovery. Training responsiveness increased due to the severity of motor deficits, whereas spared attentional abilities, especially visuospatial attention, supported motor improvements.

Considering the integration of motor and cognitive systems underlying motor learning (Piron et al., 2009), it is important to exploit their functioning at a neural level in stroke patients. Novel approaches for motor rehabilitation with technology-based techniques aim to resemble the ecological environments, where behaviour is demanding, and cognitive abilities may be involved (Piron et al., 2009; Krakauer, 2006). It is currently recognised in neurophysiology that the observation of actions performed by others activates the same neural structures responsible for the actual execution of those same actions. AOT exploits this neurophysiological mechanism to recover motor impairment: patients observe a daily action and hereafter perform it. Areas gifted with this action observation–action execution matching mechanism are defined as the mirror neuron system. During action observation video, the maintenance of attention is perhaps facilitated. Motor imagery, together with AOT, can be intended as a "cognitive rehabilitation tool" and plays a significant role in motor learning, activating MNS regions that are implicated in motion preparation and execution (Lotze & Cohen, 2006). Mao and colleagues (2020), studying the clinical effects of the AOT in stroke patients, demonstrated that activation of the MNS by AOT positively impact motor and cognitive recovery. Specifically, they discovered that AOT improved patients' concentration and the ability for mental multitasking. The areas implicated in these functions coincide with MNS distribution in the prefrontal cortex and temporal gyrus. Furthermore, they clinically notice that patients with attention deficit have difficulty understanding and collaborating with the therapist, resulting in a poor rehabilitation outcome (Mao et al., 2020). Thus, concentration and attention in general, are cognitive functions that play a crucial role in the functional recovery of the upper limbs.

It is known that the role of engagement is crucial for improving neuroplasticity and to promote functional recovery in patients with neurological disorders (Danzl et al., 2012, Phillips, 2017). In our study, patient engagement was positively associated with the accuracy of interactive computerized exercises, therefore considering itself a potential predictor of concentration, defined as the ability to focus on the task performed while ignoring distractions. In a systematic review of Sarasso et al. (2015), a lack of evenness on duration and frequency of AOT it was emerged, making still today difficult to determine an optimal posology. The features of training, expressed as mean values (range) were: 6 sessions a week (3–10), 16.2 days (1-40) of duration of treatment, 12.4 min (5-30) for each session, 16.9 min of observed actions performance (5–36). In our study, the trend for accuracy during the four weeks of training for all patients shows sustained improvement up to the third week and then decays. This could be justified by the longer than average length of treatment, which may have become monotonous, thus leading to a loss of attention and commitment. Considering the total sample, all patients showed an overall accuracy's difference specifically between week 1-week 2, week 1-week 3, week 3-week 4, demonstrating that engagement and attention improve, evidently due to the alternative treatment, more fun and dynamic, then stabilize and decay. The most frequent duration of each video is between 3 and 10 min; seems that videos lasting 5–6 min appear to be the most proper approach to obtain a good equilibrium between patients' sustained attention and training efficacy (Sarasso et al. 2015). Then, the subgroups in the total accuracy over the four weeks of AOT show a significant difference: the group without attention deficit shows higher performance. More specifically, considering the accuracy for each week of treatment, the difference between the two subgroups emerges only in week 3 and week 4. The attention deficit group indeed exhibits worse performance. Nevertheless, the overall adherence to AO training was high; no participant dropped out. However, the level of engagement was statistically difference between the subgroups: the group without attention deficit reported a higher level of engagement in AO training than the group with deficit; the patient's basic engagement appears to be determined by their emotional state and level of cognitive functioning (Lequerica et al., 2009; Bright et al., 2015). Engagement is a complex concept with multiplex meanings (Barello et al., 2014; Bright et al., 2015): an observable patient behaviour similar to compliance or an interactive interpersonal process. Patient's engagement was negatively associated with attention deficit, as mean that a good level of attention predict a better perception of patient's engagement. Perhaps, the perception of having a cognitive deficit leads to being less incentivize in the treatment. In our sample, the attention deficit group describe the AO training as less motivating and stimulating and perceived a minor sense of accomplishment and gratification. The same group reported major difficulties in focused in the training, describing the duration of daily session less adequate and more mentally demanding. They perceived the training less fun, energising, and less pleasurable and not interesting to repeat it at home.

Patient engagement is indispensable to achieve highest benefits from rehabilitation (Kortte et al., 2007; Medley & Powell, 2010). It was observed that by growing patients' attention and interest toward rehabilitation training, there is an updating and modification at a neurological level, which leads to ameliorate functional outcomes (Moucha & Kilgard, 2006). Patient's engagement have been described as a "process-like and multi-dimensional experience, resulting from the conjoint cognitive (think), emotional (feel), and conative (act) enactment of individuals toward their health management" (Graffigna et al., 2013). It is a key element in making them feel like participants in the treatment process that will lead to improve patient sensitisation, knowledge, and empowerment and finally the therapy's adherence (Fisher et al., 2011). Furthermore, engagement is frequently co-constructed within patient-practitioner relationships; indeed a practitioner's attitudes and behaviours may affect patient engagement (Barello et al., 2014; Bright et al., 2015) and how practitioners operate with their patients (Meltzer et al., 2009). While there has been reasonable attention to patient engagement in rehabilitation, there has been little consideration of practitioner engagement and this is a gap that must be resolved for optimizing the neurorehabilitation setting, thus their efficacy.

Our experiment has some limitations, which can be improved by further studies. Firstly, this study used a small sample size; it would be useful to expand the sample. Secondly, excluding the attentional domain, the patients underwent tailored neuropsychological assessments that prevented the standardized evaluation of a broader range of cognitive domains. Furthermore, the lack of neuropsychological evaluation at the end of treatment to identify an eventual improvement not only in motor but also in cognitive area. It would be useful to assess the level of practioner's engagement and the level of engagement with the AOT also from a group of control patients that doing conventional or another type of intervention. It could be proposed also the AOT in small group; competition, challenge, and working with peers increase intrinsic motivation in educational environments. Future studies should collect information on a broader range of neurophysiological index of attention; the use of neurofeedback methods would be strengthen the generalization of our findings. A real-time EEG marker for attention and for engagement could provide information about the temporary functional change induced by the motor treatment session. The integration of behavioural and neurophysiological information is a valuable approach to understand and tailor upper limb motor treatment in stroke patients. The possibility of predicting rehabilitation outcomes might inform clinical decisions on the intervention program, thereby optimizing resources and fostering patients' recovery.

3.5 Conclusion

The present study aimed to integrate clinical and behavioural data as predictors of upper limb motor recovery, exploiting a relatively small but selected sample of patients that consistently received AOT motor rehabilitation. Results showed that AOT improved not only motor and functioning ability but also attentional level. Moreover, attentional abilities are associated with the level of patient's engagement, with interactive computerized exercises accuracy (i.e. concentration measure) during the treatment and finally with a better score motor rehabilitation increment. The integration of motor and cognitive variables is crucial to understand patients' variability in rehabilitation: attention deficits could play a key role into motor recovery of the upper limb, supporting rehabilitation's engagement and outcomes.

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THE MULTIFACTORIAL NATURE OF DISABILITY AND HEALTH-RELATED QUALITY OF LIFE AFTER STROKE: A 6-YEARS FOLLOW-UP STUDY

ABSTRACT

Objective: This study aims to identify demographic and clinical factors that influence disability and health-related Quality of Life (HR-QoL) at the end of rehabilitation in subacute stroke patients and at short-term (6 months) and long-term follow-up (6 years).

Methods: This is a secondary analysis of a randomized controlled trial. Thirty-nine stroke survivors (62% male, mean age 68y) were assessed using the Stroke Impact Scale (SIS) before, after three weeks, at the end of rehabilitation (6-week), after 6-months and six years. SIS domain scores were calculated over time in relation to age, sex and stroke severity. Long-term changes were explored through clinically meaningful changes of SIS-16 (physical SIS).

Results: An overall improvement was found after the rehabilitation in all SIS domains except Memory and Thinking Ability, Emotions and Communication. Baseline SIS-16, presence of a sensory deficit and patient's setting were factors related to SIS-16 at the end of rehabilitation and after 6 months. Mobility, Strength and Hand Functionality were the most deteriorated domain after six years. Patients with higher stroke severity, males and ≥ 65 years, experienced a higher impact in all domains, revealing more difficulties in daily life. Participants had a significant minimal clinically important difference in every SIS-16 domain, except for Hand Function.

Conclusion: Disability and HR-QoL improved after rehabilitation but deteriorated years after stroke. Stroke severity, male gender and older age are all factors that influenced disability and HRQoL. Consequently, multidisciplinary, long-term stroke management is warranted to reduce the impact on stroke patients.

Keywords: Rehabilitation; Stroke; Stroke Impact Scale; Health-related Quality of Life.

4.1 Introduction

Though stroke-related deaths are decreasing, the prevalence of individuals living with post-stroke effects has grown due to the increase and ageing population (GBD 2016 Stroke Collaborators; 2019). Stroke patients have a wide range of impairments and a broad spectrum of symptom severity and sequelae. Mobility impairment, increased dependence in activities of daily living, sensory, cognitive, perceptual, communicative and emotional deficits with mood alterations and social alienation have been reported even at a chronic stage (Guidetti et al., 2014; Middleton et al., 2014; Ytterberg et al., 2017; Bertani et al., 2017; Doli et al., 2017; Carey et al., 2018).

Stroke survivors' lives are affected in multiple ways and may not be delineated entirely by only health and functional status; the global concept of Quality of Life (QoL) should be considered when assessing a stroke patient, as it may effectively be degraded. The consequences of Stroke and health status affect even mild strokes (Duncan et al., 1997; Terrill et al., 2018; Morsund et al., 2019; Vlachos et al., 2021).

A multidimensional approach is necessary to measure disability and QoL. The World Health Organization (WHO) suggests that a global view of the QoL includes physical and psychological health, social relationships, and environmental quality (World Health Organization; 1996). The Barthel Index (BI) and the Rankin Scale are the most habitual outcome measures used in stroke research, focusing on stroke disability and motor recovery after stroke (Quinn et al., 2017; Askim et al., 2018; Chang et al., 2020; Chien et al., 2020; Cinnera et al., 2020).

The Stroke Impact Scale (SIS), can be used to measure disability and health-related QoL after stroke. This self-reported instrument evaluated the effects of Stroke, focusing on physical, emotional and everyday life aspects (Duncan et al., 1999). It has been extensively used as the outcome measure to define the extent and domains of improvement after stroke rehabilitation (Stuart et al., 2009; Lin et al., 2009; Lo et al., 2009; Sullivan et al., 2014; Bunketorp-Käll et al., 2017; Askim et al., 2018; Skoglund et al., 2019).

Recognizing predictors of QoL can serve to define an optimal overall treatment that improves physical function while maximizing the QoL of stroke survivors. In this regard, physical, psychological and social factors have been considered necessary in predicting QoL after stroke (Teoh et al., 2009; Mahesh et al., 2018; Boudokhane et al., 2021).

Stroke patients and their families observe difficulties in functioning in daily life for a considerable time following Stroke. Generally, rehabilitation intervention focus on the first three months after stroke onset (Bergström et al., 2011; Ekstam et al., 2007; Lui et al., 2018). However, several studies demonstrate the need for rehabilitation is not always fulfilled by 12 months (Legg et al., 2007; Tistad et al., 2012: English et al., 2019; Schindel et al., 2021), especially in a patient with moderate or severe Stroke (Tistad et al., 2012). Indeed, studies reveal that one year or more following Stroke, there is a negative impact on an individual's Quality of Life, Hand Function, Strength (Carod-Artal et al., 2008; Hartman-Maeir et al., 2007; Guidetti et al., 2014), Activities of Daily Living (ADL) and Social Participation (Muren et al., 2008; Guidetti et al., 2014).

A variety of studies have used the SIS to investigate stroke impact, but a paucity examined the perceived impact of a stroke at different time-points following a stroke event (Duncan P, Wallace et al., 1999; Lai SM, Studenski et al., 2005; Carod-Artal et al., 2008; Hartman-Maeir et al., 2007; Muren et al., 2008; Susanne et al., 2012; Ytterberg et al., 2017).

Therefore, a better understanding of the perceived change over time to deliver rehabilitation interventions with appropriate timing is needed (Guidetti et al., 2009). Rehabilitation has to meet personal needs and expectations to improve the quality of life of stroke patients. This approach could be as contribute to the optimal allocation of healthcare resources. Information about the perceived impact of a stroke may help individualizing the rehabilitation provided. Thus, the goals of this study were to examine global and domain-specific disability and health-related QoL in subacute stroke patients after rehabilitation and at short-term and long-term follow-up. Secondly, we aimed to explore the influence of several factors (age, gender and stroke severity) on disability and health-related QoL after Stroke.

4.2 Methods

This is a secondary analysis of a prospective, randomized, single-blinded, control study that compares a technology-based arm rehabilitation (robot-assisted arm therapy + hand functional electrical stimulation) with an intensive conventional arm therapy (NCT02267798) (Straudi et al., 2020). The local Ethics Committee approved the study, and a written consent was obtained from each participant. All procedures were conducted according to the ethical standards of the Declaration of Helsinki.

The inclusion criteria were (a) aged 18-80 years, (b) diagnosis of first, single unilateral ischemic Stroke verified by brain imaging <8 weeks, (c) an upper limb motor impairment defined by an upper extremity score >11 and <55 on the Fugl-Meyer Assessment (FMA-UE), (d) no severe cognitive deficits as defined by a score of more than 21 on the Mini Mental-State Exam. Participants with physician-determined major medical problems or poor physical conditions were excluded to eliminate the potential confounding effects of comorbid medical conditions on the study results. Patients with impaired ability to understand the questionnaire because of severe aphasia were also excluded.

Eligible participants were randomly assigned to one of 2 treatment groups. The experimental group received a unilateral, proximal arm robot-assisted therapy combined with hand functional electrical stimulation (RAT+FES); the control group received intensive conventional therapy (ICT). All participants received a 1 hour and 40 minutes session, five times weekly, for a 6-week duration. The presence/absence of transcranial magnetic stimulation (TMS) induced motor-evoked potentials (MEPs) was also measured. Focal TMS was performed by means of a 70-mm figure-of-8 stimulation coil connected to a Magstim Bistim (The Magstim Company, Carmarthenshire, Wales, UK), producing a maximum output of 2 T at the coil surface. The resting motor threshold was determined by holding the stimulation coil over the optimal scalp position defined as the position from which MEPs with maximal amplitude were recorded for opponent (OP) muscle. The patient was classified as MEP+ if MEPs were observed with a consistent latency in response to at least 5 stimuli, with OP latencies ≈ 20 – 40 ms. Barthel Index (BI) score at admission was used to determine stroke severity: BI scores of 100–50 signified a mild stroke; 49–15 a moderate stroke; and ≤ 14 a severe stroke (Mahoney & Barthel; 1965).

The Stroke Impact Scale (SIS) was used for assessing disability and health-related QoL. The SIS Version 2.0 (Duncan et al., 1999) consists of 64 questions divided into eight domains, including Strength, Hand Function, Mobility, Activities of Daily Living/Instrumental Activities of Daily Living, Memory, Communication, mood and social Participation. The number of questions in each domain ranges from 4 to 11, with scores varying from 5 to 1, according to the degree of difficulty, amount of time and strength needed, depending on the dimension. The higher the score, the better the quality of life. Four of these dimensions (Hand Function, Mobility, Activities of Daily Living and Instrumental Activities of Daily Living) can be evaluated together to form a single domain called the physical domain (SIS-16) (Duncan et al., 2003b). The SIS also includes a question to assess the patient's global perception of the percentage of the recovery. After the SIS is administered, the respondent is asked to rate their per cent recovery since their Stroke on a visual analogue scale of 0 to 100, with 0 meaning no recovery and 100 meaning full recovery. In stroke patients with cognitive or communicative impairments that limited the ability to provide self-reports, their caregiver was invited to develop a proxy version. Agreement between the individuals with Stroke and the proxies is acceptable in most of the SIS domains (Duncan et al., 2002). SIS has been evaluated as a reliable, valid, and sensitive outcome measure for measuring meaningful functional outcomes and comprehensive measure of HR-QoL in stroke patients (Duncan et al., 1999; Duncan et al., 2003a; Duncan et al., 2003b).

In the present study, we consider the clinically important differences (CIDs) of the four physical domains of the SIS: 9.2 points for Strength, 5.9 points for ADL/IADL, 4.5 points for Mobility, and 17.8 points for Hand Function (Lin et al., 2010) between 6 months and 6 years. In line with previous recommendations (Lin et al., 2010) the participants were sorted into 3 groups according to changes in their SIS physical domain scores between T3 and T4 follow-up: clinically significant positive change (≥ CIDs); clinically significant negative change (≤ CIDs); and no change (if between – CIDs and + CIDs).

Interviews were performed by an investigator blinded to the treatment group before intervention (T0), after three weeks (T1), at the end of treatment (6weeks, T2), at 6-month follow-up (T3) and 6 years (T4) follow-up.

Data Analysis

Descriptive statistics were used to describe the study sample and their responses on the SIS at T0, T1, T2, six months (T3) and six years follow-up (T4). According to variables distribution, verified through a Shapiro-Wilk test, these characteristics were reported as mean and standard deviation, median and interquartile range, or frequency and percentage. Aggregated scores in each domain of SIS were generated using the algorithm ([((real score – lower possible score)) x 100] / possible score amplitude) (Ware JE, 1993). Correlations were performed between the personal (i.e. age, sex, setting), clinical factors (i.e. stroke severity, cognitive/sensitive deficits, comorbidities), SIS domains, using Spearman's rank correlation coefficient (Rho). A linear regression model was used to underline variables that predicted the SIS-16 at different time points (dependent variable).
A repeated-measures analysis of variance (RM-ANOVA) ($p < 0.05$) with Time (4 levels: T0, T1, T2, T3) as within-subject factors and type of treatment (2 levels: ICT or RAT+FES) as between-subject factor was performed to reveal a difference in SIS 2.0 domains within each group of treatment through the four time frame. Wilcoxon rank-sum test was used to explore changes in domain scores between 6 months and six years follow-up. The Mann–Whitney U test was used to examine differences in SIS scores at the T4 follow-up concerning stroke severity (mild/moderate), sex (male/female), and age (<65 or ≥65). The categorical cut-off values were arbitrarily chosen. The significance level was set at p<0.05. The software used for the analyses was STATA 13.0.

4.3 Results

391 consecutive patients with ischemic stroke were screened between January 2014 and September 2016, and 40 were enrolled in the study (median age, 68 years; 61,5% male). Participants were randomized to the two groups through a blocked randomization approach: 20 patients were allocated to RAT+FES, and 20 patients received ICT. One subject in the RAT+FES group did not receive the allocated treatment because of a post-randomization dropout. All participants concluded the rehabilitation protocols except for a subject in the RAT+FES group who withdrew because of medical issues. The 17.5% (5 in the RAT+FES group and 2 in the ICT group) did not return to the hospital for the 6-months follow-up for personal reasons (overall attrition rate, 22.5%). The two groups did not differ in demographic and clinical characteristics. Moreover, the two groups of treatment are homogeneous in the scores obtained in SIS 2.0 domains evaluated before rehabilitation treatment (T0). See *Table 1.*

Table 1. Baseline sample characteristics

		RAT + FES (n= 19)	ICT (n= 20)	TOTAL (n= 39)	*p*-value
Age (years)	median [range IQ]	68 [56 - 71]	68 [58.5 - 73]	68 [58 - 73]	0.715
Sex (Male)	n (%)	12 (63.2)	12 (60.0)	24 (61.5)	0.839
Stroke type	1 subcortical n (%)	9 (47.4)	10 (50.0)	19 (48.7)	0.344
	2 cortical n (%)	6 (31.6)	9 (45.0)	15 (38.5)	
	3 brain n (%)	4 (21.0)	1 (5.0)	5 (12.8)	
Stroke severity	Mild n (%)	13 (68.4)	15 (75.0)	28 (71.7)	0.345
	Moderate n (%)	6 (31.5)	5 (25.0)	11 (28.2)	
Stroke onset (days)	median [range IQ]	39 [21 - 62]	32.5 [20 - 51]	37 [21 - 60]	0.574
Affected hemisphere	left n (%)	13 (68.4)	14 (70.0)	27 (69.2)	0.915
Cognitive deficits	n (%)	4 (23.5)	6 (35.3)	10 (29.4)	0.452
Sensitive deficits	n (%)	4 (25.0)	5 (27.8)	9 (26.5)	0.855
N° comorbidities	median [range IQ]	1.5 [1 – 3]	2 [1 – 3]	2 [1 – 3]	0.384

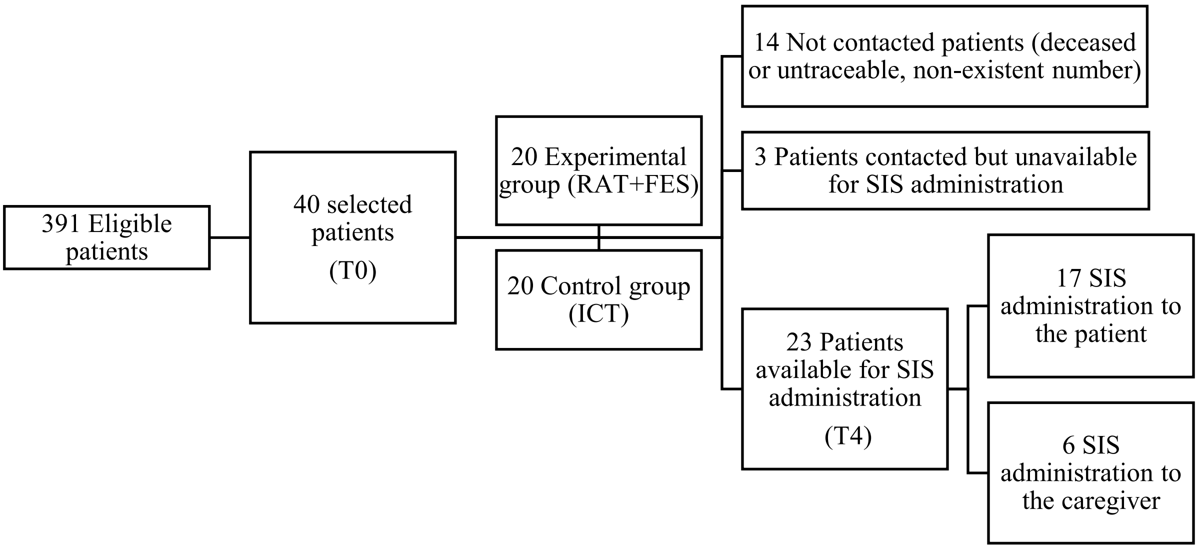
Setting	hospitalization n (%)	15 (79.0)	13 (65.0)	28 (71.8)	0.333
Strength	Mean (SD)	34.4 ± 12.4	37.5 ± 16.3	36.0 ± 14.5	0.514
Memory & thinking	Mean (SD)	87.5 ± 15.8	88.8 ± 13.7	88.2 ± 14.5	0.648
Emotions	Mean (SD)	72.7 ± 16.0	65.3 ± 16.9	68.8 ± 16.7	0.175
Communication	Mean (SD)	93.3 ± 9.6	93.6 ± 8.2	93.4 ± 8.8	0.634
ADL/IADL	Mean (SD)	42.8 ± 23.9	44.2 ± 19.1	43.5 ± 21.2	0.849
Mobility	Mean (SD)	69.7 ± 30.3	59.8 ± 27.5	64.5 ± 28.9	0.294
Hand function	Mean (SD)	11.4 ± 20.3	10.5 ± 21.5	10.9 ± 20.7	0.643
Participation	Mean (SD)	58.3 ± 25.4	44.2 ± 25.2	50.9 ± 25.9	0.093
SIS – 16	Mean (SD)	47.8 ± 20.2	42.9 ± 17.3	45.2 ± 18.6	0.421
MEPs	n (%)*	7 (50.0)	9 (60.0)	16 (55.2)	0.588

*MEPs: motor evoked potentials; RAT+FES: robot-assisted therapy combined with hand functional electrical stimulation; ICT: intensive conventional therapy; ADL: activities of daily living; IADL: instrumental activities of daily living.

The SIS 2.0 was administered by phone after almost six years from the stroke onset (mean onset=70 months, SD 8.78). 17 patients were not considered because seven were deceased, seven were untraceable, and three did not provide informed consent.

Thus, the SIS questionnaire was administered to 23 patients (61% > 65 years at stroke onset; 61% male). The Barthel Index (BI) was used to categorize stroke severity (Mahoney & Barthel; 1965): according to the BI score at T0, 17 had mild severity and seven moderate severity. Among these, 70% of patients had a lesion in the right hemisphere; 26% cognitive deficits, 35% anxious and depressive symptoms and sensory deficits. During these six years, 96% of the sample was diagnosed with comorbid disorders that emerged following the Stroke. Of 23 patients, 17 SIS2.0 questionnaires were administered directly to the patient and 6 to a caregiver due to severe cognitive impairment or poor patient cooperation. At the time of telephone contact, all patients were staying at their homes. The study flow diagram is reported in *Figure 1.*

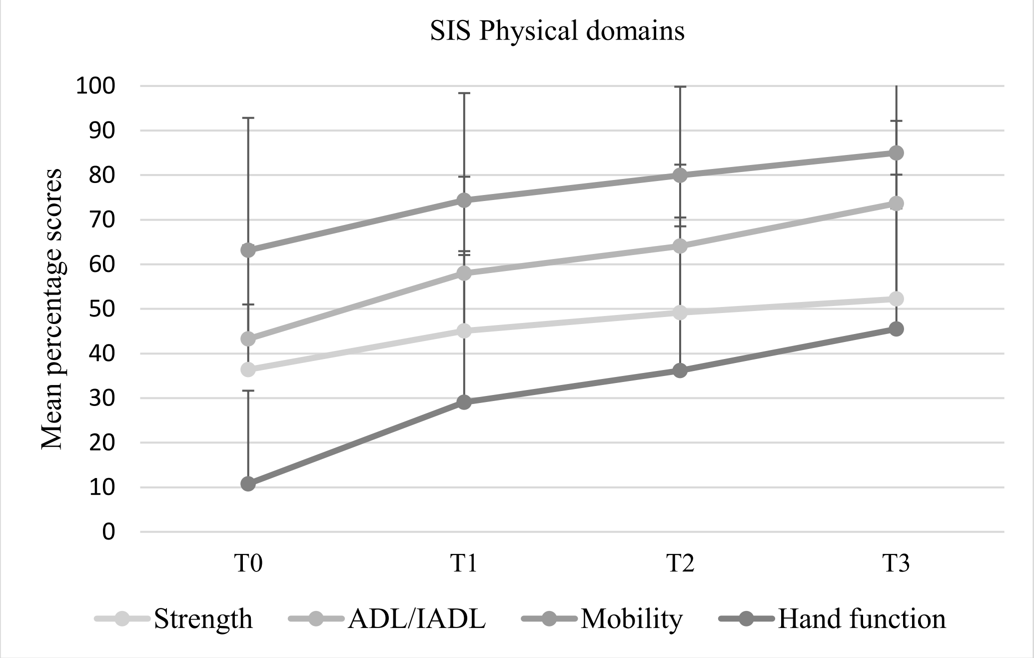
Figure 1. Study flow diagram



The impact of Stroke on short-term quality of life

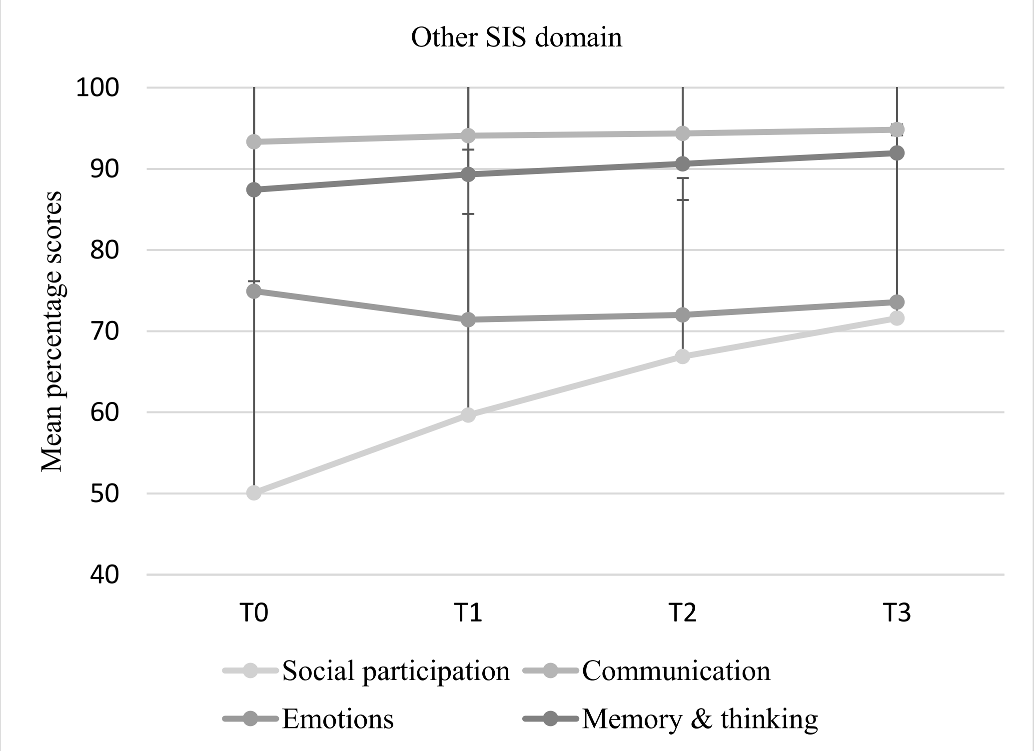
In the initial total sample (N=40), an overall improvement was found in most SIS 2.0 domains between the pre-rehabilitation period and the 6-months follow-up. The psyical domains (SIS-16) shows a greater positive improvement trend than the other domains during the four time points assessment (see *Figure 2a and b*).

Figure 2a. Mean percentage scores versus time (T0, T1, T2, T3) in SIS 2.0 physical domains



*T0 (before intervention); T1 (after three weeks), T2 (at the end of treatment), T3 (at 6-month follow-up). Data are reported as mean and standard deviation for each period.

Figure 2b. Mean percentage scores versus time (T0, T1, T2, T3) in other SIS 2.0 domains



*T0 (before intervention); T1 (after three weeks), T2 (at the end of treatment), T3 (at 6-month follow-up). Data are reported as mean and standard deviation for each period.

The RM-ANOVA confirm a significant main effect of time (p<.001), except for Memory and Thinking (p=.208), Emotions (p=.231) and Communication (p=.501); all items significantly change and increase over time (*Table 2*). Conversely, the interaction between treatment and time is never significant (p>.1).

Table 2. Analysis of variance for SIS 2.0 domains

SIS domains	Time p-value	Treatment p-value	Interaction term p-value
Strength	<0.001	0.829	0.505
Memory & thinking	0.208	0.007	0.681
Emotions	0.231	0.044	0.521
Communication	0.501	0.208	0.590
ADL/IADL	<0.001	0.115	0.664
Mobility	<0.001	0.658	0.187
Hand function	<0.001	0.292	0.817
Participation	<0.001	0.022	0.113
SIS - 16	<0.001	0.361	0.164

*ADL: activities of daily living; IADL: instrumental activities of daily living

The SIS-16 score obtained at T0 and the patient's setting is positively associated with the score obtained at T2 and T3. In contrast, the presence of sensitive deficit is negatively related to the SIS-16 T3 score. In the adjusted linear regression model, the SIS-16 score obtained at T0 is a potential predictor of the SIS-16 T2 score (β0=0.654, p=<.001) and SIS-16 T3 score (β0=0.641, p=<.001). The presence of sensitive deficit (β0=-15.7, p=.025) is considered a potential predictor of the SIS-16 T3 score. Finally, the patient setting is identified a possible predictor of the SIS-16 T2 score (β0=14.2, p=.024) and SIS-16 T3 score (β0=13.9, p=.036).

The impact of Stroke on long-term quality of life

Mean scores were lower in the sample at T4 than those collected at T3 (see *Table 3*). Strength, Hand Function and Participation domains showed the highest perceived impact (i.e. the lowest scores) at both follow-ups. The Communication domain had the lowest impact (i.e. the highest scores) at both time points. Significant changes in scores between T3 and T4 with higher reported impact at six years follow-up were seen in 3 domains: Strength (p=.002), Mobility (p=<.001) and Hand Function (p=.037).

Table 3. Perceived impact of Stroke at six months and six years, and p-values for changes in Stroke Impact Scale (SIS) domain scores

SIS domains	Six months (T3) Mean (SD)	Six years (T4) Mean (SD)	Changes between 6 months and six years, *p*-value
Strength	50.6 (20.9)	38.0 (23.8)	0.002**
Memory & thinking	92.1 (9.0)	80.6 (26.4)	0.156
Emotions	72.5 (21.8)	73.6 (20.0)	0.651
Communication	93.9 (6.4)	87.6 (16.2)	0.065
ADL/IADL	72.8 (17.9)	62.3 (33.6)	0.250
Mobility	86.1 (17.3)	61.9 (27.6)	<.001**
Hand function	41.7 (35.8)	30.2 (30.5)	0.037*
Participation	68.0 (23.6)	63.0 (27.1)	0.478
Stroke recovery		57.0 (24.2)	

*ADL: activities of daily living; IADL: instrumental activities of daily living; SD: standard deviation

The Mann–Whitney U test was used in cross-sectional analyses to examine differences in SIS scores at the T4 follow-up concerning stroke severity, sex and age. At six years after Stroke, there was a significant difference in SIS scores between persons with mild compared with moderate Stroke in most domains: those with moderate Stroke reported higher impact than those with mild Stroke. The participants with mild Stroke reported significantly higher impact in the domains Strength (p=.027) and Mobility (p=.006). About sex, men reported a higher impact on Memory and Thinking Ability (p=.0123) and Hand Function (p=.015). Furthermore, persons ≥ 65 years reported higher impact in the Mobility domain (p=.046) (see *Table 4*).

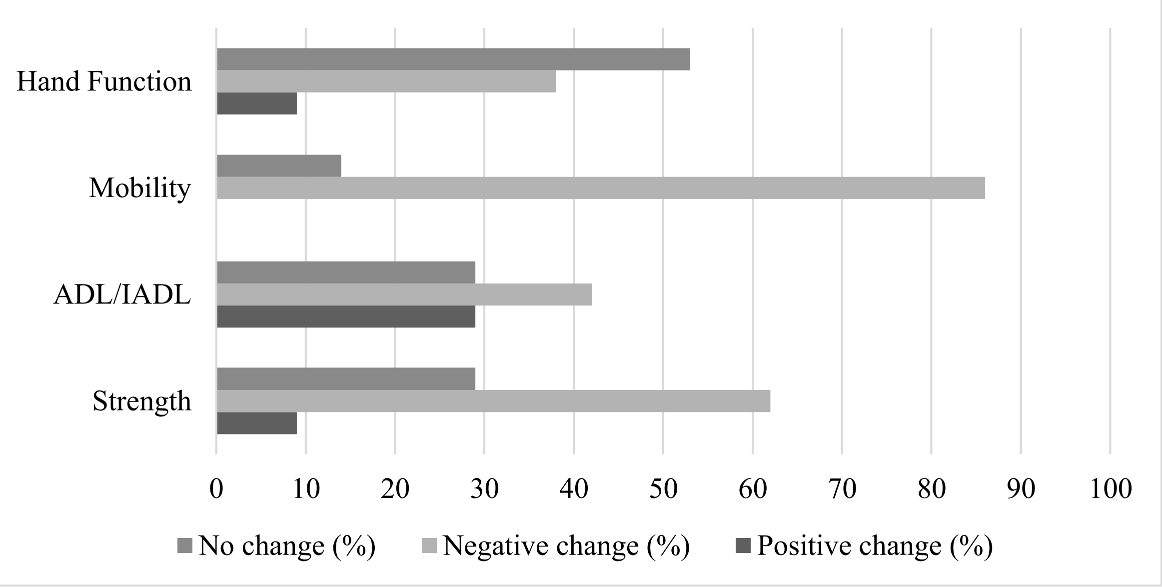
Table 4. Factor influencing health-related Quality of Life and disability after stroke

	Stroke severity			**Sex**			**Age**		
SIS domains	Mild Mean (SD)	Moderate Mean (SD)	*P* Value	Male Mean (SD)	Female Mean (SD)	*p* Value	<65 years Mean (SD)	≥65 years Mean (SD)	*p* Value
Strength	44.49 (21.64)	19.79 (21.07)	0.0278*	34.38 (22.30)	43.75 (26.15)	0.4064	40.97 (21.45)	36.16 (25.73)	0.678
Memory & thinking	86.76 (18.64)	63.02 (38.14)	0.0966	70.31 (29.51)	96.53 (5.51)	0.0123*	87.5 (19.76)	76.12 (29.74)	0.2553
Emotions	74.84 (19.97)	69.91 (21.55)	0.5273	71.83 (15.78)	76.23 (26.14)	0.2827	80.25 (13.85)	69.25 (22.55)	0.2423
Communication	90.55 (12.11)	79.17 (23.84)	0.1861	83.93 (19.19)	93.25 (7.87)	0.3511	93.65 (9.07)	83.67 (18.73)	0.1571
ADL/IADL	70.71 (27.71)	38.54 (40.07)	0.0537	58.18 (36.36)	68.75 (29.81)	0.5916	77.08 (28.05)	52.83 (34.40)	0.0583
Mobility	71.76 (22.29)	33.75 (22.12)	0.0063*	61.96 (28.83)	61.67 (27.39)	0.8008	75.28 (25.87)	53.21 (25.99)	0.0469*
Hand function	32.65 (31.53)	23.33 (28.75)	0.4956	17.14 (23.10)	50.56 (30.36)	0.0155*	32.78 (24.76)	25.57 (34.44)	0.4198
Participation	67.32 (26.82)	49.44 (27.94)	0.2241	58.55 (26.24)	70.06 (29.37)	0.3001	63.89 (23.24)	62.82 (31.01)	1
Stroke recovery	60 (20.32)	47 (35.28)					57.22 (20.63)	56.92 (27.2)	

*ADL: activities of daily living; IADL: instrumental activities of daily living; SD: standard deviation

As reported in *Figure 3*, the highest proportion of negative clinically meaningful changes between 6 months and six years follow-up was found in the domain Mobility (86%) and Strength (62%). On the other hand, 29% of the participants had a positive clinically meaningful change in ADL/IADL domain. More frequently, no positive or negative change was found between T3 and T4 in domain Hand Function (53%).

Figure 3. Percentage of negative, positive and no changes in SIS-16 between 6 months and six years follow-up



*ADL: activities of daily living; IADL: instrumental activities of daily living

4.4 Discussion

The main findings of this study are that disability and health-related QoL increased after rehabilitation and within a short-term follow-up, without any significant differences between different rehabilitation protocols as previously reported (Van De Port 2012, Conroy 2019, Ahmad 2019). Conversely, they deteriorated at a long-term follow-up. Overall, it is assumed that rehabilitation is useful and contributes to reducing the impact of Stroke on QoL and the improvement of SIS scores in the subacute phase presents only a temporal correlation. The most significant increase is in the physical domains. On the contrary, Memory and Thinking, Emotions and Communication domains remain almost constant. Emotion regulation is impaired following Stroke, with implications for social participation and recovery (Cooper et al., 2015). Ostir et al. (2008) reported positive emotion on stroke survivors in the initial months following a stroke, thus denoting adults' emotional resilience when faced with health defiance. The positive attitudinal behaviour towards disability confers better role limitation due to the emotional problem domain. Interestingly, stroke survivors who have accepted their disability are less likely to develop depressive symptoms, which positively predicts emotional adaptation after stroke (Oyewole et al., 2020). Most of the studies that investigated the impact of stroke have shown that the physical domains are the most affected and have more persistent sequelae over time. In particular, the SIS captures persisting difficulties in Hand Function, ADL / IADL and overall physical function-SIS 16 (Lai et al., 2002).

In this study, the first predictor of outcome was the baseline value of SIS-16, which is positively correlated with the SIS-16 score at the end of treatment and six months follow-up. This indicates that greater physical health perceived by the patient in the subacute phase is associated with a higher QoL in the months following the event. This is a considerable achievement and it would be possible to understand the needs and the real targets for improvement, then define a targeted management of the patient through this instrument. Another predictor of outcome is the patient's rehabilitation setting. It was found that patients that receive inpatient rehabilitation experience more significant impairment and disability; in contrast, living at home is positively associated with SIS-16 at the end of rehabilitation and at first follow-up. It is deduced that such patients experience better recovery in familiar contests: living at home was able to perform daily living activities at a higher level. Furthermore, living in their environment permit to generalize the restored functioning in ambulatory. Moreover, getting patients to their normal lives could improve mood and psychological well-being, perhaps due to family closeness or caregiver. Somatosensory deficits represent a common sequela of Stroke, affecting about 50-80% of survivors. They have been shown to influence and worsen physical outcomes, particularly somatosensory and motor skills, functional performance and social participation in the short and long term (Kessner et al., 2016). This study showed a negative correlation with SIS-16 at follow up; that signify these patients experience more disability and health-related QoL than those with no sensory deficit.

Our results suggest that the SIS domains most deteriorated after 6-years are Strength, Mobility and Hand Function. The same emerged from other studies that used the SIS and carried out the follow-up at 3, 9 and 12 months following stroke (Coral et al., 2008; Lai et al., 2003; Susanne et al., 2012). Nevertheless, these are the same domains for which there was a more significant increase in the six-month follow-up. There is therefore an improvement during rehabilitation, and then occur progressive deconditioning. This supports the frequent problem of lack of movement and physical activity in the chronic patient and learned disuse (Han et al., 2017).

The functional independence assessed by the BI is a determining factor on the long-term outcome (Jørgensen et al., 1995; Huybrechts et al., 2007). A relationship between the Barthel Index and recovery was observed – a decrease of BI scores is associated with a worse long-term prognosis. Other studies display that stroke severity negatively affects the patient's quality of life even years after the acute event (Chou et al., 2015; Ramos-Lima et al., 2018).

The present study found that six years later, stroke survivors of moderate severity had lower scores in most SIS domains than those who had mild Stroke; the difference is significant for the Mobility and Strength domains. However, even mild stroke patients experience a negative impact on QoL even six years later. It was demonstrated that HRQoL appears to be good enough for the majority of patients six years post-stroke; indeed, despite the prominent ongoing physical invalidity, stroke survivors seem to adapt well psychologically to their disease (Hackett et al., 2000).

Regarding patient sex, females showed higher scores than males in most SIS domains; however, the difference is highly marked in memory and thinking and Hand function domains. Various studies (Gargano & Reeves; 2007; Gray et al., 2007; Almborg et al., 2010; Singhpoo et al., 2012; Bushnel et al., 2014), but not all (Kauhanen et al., 2000; Jönsson et al., 2005; Muus et al., 2010; Haley et al., 2011) have reported worsening of QoL after Stroke in women relative to man.

Wang & Langhammer (2018) reported that the sex gap and its importance in recovery in post-stroke QoL are not well defined; further studies are needed to fill this uncertainty.

Relative to age, lower scores are reported for older subjects (> 65 years old) in all SIS domains. It is therefore hypothesized that after years from the acute event, younger patients develop higher QoL. This could be related to a reduction in self-efficacy and resilience that occur with advancing age (Salbach et al., 2006), but further analysis on this aspect is needed.

As evidenced by Ytterberg et al. (2017), in our study, both categories of age of patients experience a similar perception of stroke recovery equal to 57%.

The results obtained at six years, in accordance with Aziz's review (2010), show the need for longer-lasting rehabilitation interventions. Rehabilitation encompasses physical intervention and should address all aspects of everyday life, including psychological well-being and social participation. Although physical function has deteriorated, stroke patients can adapt to the new life situation and their quality of life in socio-emotional and mental domains improved during the years. The importance of interventions aimed at improving work and social commitment is recognized, due to the weight these aspects have on the quality of life during post-stroke recovery (Tse et al., 2017).

More generally, therefore, it would be necessary to take multidisciplinary care of patients even years after the acute event and better manage the patient in the community.

Patients with higher stroke severity, male and ≥ 65 years, experienced a higher impact in all domains; it could be possible that these categories of patients need major support with multidisciplinary approach.

There are several limitations concerning the study sample that might limit the generalizability of the study results to the population of all stroke survivors. The main limitation of the study is represented by the small size of the sample analysed. Furthermore, by carrying out a follow-up six years after the acute event, it is reasonable to consider that older individuals with a stroke of medium-severe severity may be underrepresented. This group of patients could have died in a higher percentage or have a condition too poor to be appropriate to ask them to participate in the study. This could explain the reduction of the sample from the first to the second follow-up (6 months-6 years) and the presence at T4 of only patients with mild-moderate stroke outcomes.

As having a stroke increases the risk of having a new stroke, the participants in the study might also have had new strokes over the 6 years, which might have impacted their ratings on the SIS.

The physiological ageing of patients and the possible diagnosis of new comorbidities over the years could also represent a confounding element that worsens the perception of quality of life.

However, the study's design is a strength; the 6-year follow-up after stroke and the examination of the perceived impact of Stroke over this prolonged period. The SIS scale is sensitive to changes over time. However, to the best of our knowledge, no studies analyse its sensitivity over an extended time frame.

Furthermore, data collection was conducted via telephone interviews performed by specially trained research assistants. This mode of administration has previously been validated (Kwon et al., 2006) but present some limits as private security.

Another limitation is the presence of additional "confounding" factors that can influence QoL and have not been considered. Among these: environmental factors, family support, the type and quality of the rehabilitation service (Nuttaset Manimmanakorn et al., 2008; Kwok et al., 2011).

Another confunding factor is represented by modality of SIS administration. Nevertheless, Carod-Artal et al. (2009) report an adequate agreement between stroke patients and caregivers for most SIS domains. Seems that the level of agreement may differ depending on the type of construct measured; indeed the level of agreement is major for the assessment of physical abilities and ADL, while poor agreement may be observed for the psychosocial domains of the HRQoL measures.

Finally, the SIS administration and data collection were carried out during the COVID-19 pandemic that may has negatively impacted various physical, psychological and social aspects. For the older age group, both for persons resident at home or in residential care facilities, the need for social support, liveliness, daily functioning and caregivers became limited (Prete et al., 2020; Mukhtar, 2020; Vahia et al., 2020).

4.5 Conclusion

During rehabilitation and up to six months, there is an improvement in disability and health-related QoL that tends to decrease in the following years, with a more marked worsening in the physical domains. The reduced quality of life and the perceived long-term impact after stroke highlight the importance of adequate rehabilitation interventions even years after the acute event and of lasting care of the patient, setting up community-based rehabilitative and vocational interventions. The SIS that encompass mental health, mobility, ADL, IADL, and social functioning is recommended to evaluate the recovery process following Stroke. By these measures, areas that require individualized long-term disability intervention can be determined, and patient quality of life can be maximized. Finally, researchers and clinicians cannot underestimate the impact of stroke in the long term, even considering the social and economic implications of sequelae of stroke in society. The present study can be considered a starting point for future research and clinical application in Italy contest. Extending the current investigation with a larger sample size and considering the baseline score in future research is warranted.

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TELEREHABILITATION IN ITALY DURING THE COVID-19 LOCKDOWN: A FEASIBILITY AND ACCEPTABILITY STUDY

ABSTRACT

This study examined the feasibility and acceptability of a telerehabilitation program during the COVID-19 pandemic in a sample of adult patients with physical disabilities. Of the twenty-three patients enrolled, 11 agreed to participate in a video- based telerehabilitation program. Barriers and facilitators to the adoption of telerehabilitation were identified and clinical, demographic, and psychological variables were analysed as predictors of success. Age, cognitive reserve, and resilience were significant predictors of satisfaction with telerehabilitation ($p<0.05$). The telerehabilitation program was perceived as feasible and was well accepted by patients, despite some technology challenges. However, patients who took advantage of telerehabilitation perceived differences in the quality of service and preferred traditional in-person treatment to service delivery via telerehabilitation.

***Keywords**:* COVID-19, Disability, Physical therapy, Physiotherapy. Technology, Telemedicine, Telerehabilitation.

5.1 Introduction

The World Health Organization declared the Severe Acute Respiratory Syndrome - Coronavirus – 2 (COVID-19) outbreak a Public Health Emergency of International Concern on January 30, 2020. The COVID-19 pandemic so overwhelmed Italy's healthcare system that on March 8, 2020, the government implemented containment measures. Italy was the first European Union (EU) country to adopt a precautionary generalized lockdown. This necessitated the adoption of new strategies to continue to provide rehabilitation activities.

One of the most worrying aspects of the COVID-19 pandemic was its impact on persons who were frail and vulnerable, as the virus most negatively affected persons with pre-existing chronic illnesses and physical disabilities (Bartolo et al., 2020; Boldrini et al., 2020a; Leocani et al., 2020). While persons with pre-existing conditions suffered psychiatric distress ascribed to the spread of COVID-19 (Wang et al., 2020; Holmes et al., 2020), little change was observed in symptoms of depression, anxiety, and quality of life during COVID-19 lockdown in patients with progressive multiple sclerosis (Chiaravalloti et al., 2020).

Persons with physical disabilities faced several problems during the pandemic. Communications with healthcare professionals and the delivery of a coordinated multidisciplinary rehabilitation service were interrupted or limited. Also, there was pervasive anxiety that rehabilitation treatments would not be available if the pandemic intensified, or new variants of COVID-19 emerged (Boldrini et al., 2020b).

During the COVID-19 emergency, the delivery of many healthcare services was shifted from in-person treatment to telemedicine (Hilty et al., 2013) and telerehabilitation. Telerehabilitation is an off-shoot of telemedicine that leverages telecommunication technologies to deliver rehabilitation services synchronously and/or asynchronously to patients at a distance, thereby minimizing travel time and costs (Brennan et al., 2010). These technologies, including telemonitoring, teleassistance, among others, and its branches, fall within the realm of digital physical therapy practice (Dantas et al., 2020).

The Italian Society of Physical and Rehabilitation Medicine (SIMFER) webinar held on April 3, 2020 focused attention on telemedicine applications for outpatient rehabilitation (Negrini et al., 2020). Consensus was reached among the physicians that telemedicine could and must be a common practice, especially for screening, distance support, follow-up, and in emergency situations. The experiences described by these professionals were heterogeneous in terms of the populations, intervention types, technologies used, and the applicability of telemonitoring. The perceived potential benefits included an impact on the reduction of isolation, increased motivation and compliance during sessions, and the reduction of barriers for frail and less independent persons to access consultations and treatments. However, some held onto the opinion that telemonitoring will never replace the in-person encounter between the patient and the professional who cares and provides a biopsychosocial holistic, helpful, in-person encounter.

Several barriers (i.e., technology or patient factors) can limit the safe use of telerehabilitation by healthcare institutions. These include data privacy, patient safety, and reimbursement (Negrini et al., 2020; Leochico, 2020). Health care providers' acceptance of technology is a key element that influences the sustainability and success of telerehabilitation (Brewster et al., 2014; Wade et al., 2014). Other technical barriers that can affect the adoption of telerehabilitation by healthcare institutions include low expertise in using specific hardware and software (Jafni et al., 2019).

Patients also experience technology related barriers to successful participation in telerehabilitation. These may include limited technical resources, absence of devices at home, and slow Internet bandwidth (Negrini et al., 2020; Leochico, 2020). In addition to these technical challenges, other limitations relate to patients' characteristics and behaviors, given that high levels of physical, emotional, and cognitive efforts are necessary to be engaged in telerehabilitation (Theodoros, 2012). Even though the presence of chronic medical comorbidities and reduced activities of daily living (ADL) were not detrimental to the use of technology in older adults, depressive and anxiety symptoms and other indicators of social integration and social support were significantly associated with Internet use (Choi et al., 2013).

Another possible barrier to the use of telemedicine is patient age (Negrini et al., 2020; Leochico, 2020). Di Giacomo et al. (2013) posited that the ability to use smart technologies may be negatively affected by the impact of aging on cognitive and emotional characteristics. Previous studies described a positive association between computer use and cognitive function in older adults (Czaja et al., 2006;

Tun & Lachman, 2010; Fazeli et al., 2013) suggesting that older adults with better cognitive abilities are more likely to use up-to-date technology (Slegers et al, 2012, Wu et al., 2019). Educational level, as part of cognitive reserve, can be another determinant of successful technology use in older adults (Choi et al., 2013) and in patients with Parkinson disease (Dias et al., 2016). Specifically, higher-educated people tended to acquire new knowledge most effectively (Meyer et al., 2015).

The primary aim of this study was to assess the feasibility and acceptability of a telerehabilitation program during the COVID-19 lockdown in a sample of adult patients with physical disabilities. Secondly, given that there is limited information on potential predictors of successful participation in telerehabilitation programs, demographic, clinical, and psychological variables were examined.

5.2 Methods

This cross-sectional study was performed at the Neuroscience and Rehabilitation Department of Ferrara University Hospital (Italy). The study was approved by the AVEC Ethics Committee. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines were followed in this study.

Patients were enrolled if they met the following inclusion criteria: (1) adult female or male; (2) age between 18 and 80 years; (3) presence of physical disabilities; (4) participating in an outpatient rehabilitation program that was interrupted due to COVID-19 government restrictions. We excluded patients with severe cognitive impairment that would have precluded obtaining informed consent and completing questionnaires. Demographic and clinical data were recorded: gender, age, education, nationality, housing situation, presence of a caregiver, employment, diagnosis, number of falls during the lockdown, number of calls to the General Practitioner and other physicians during lockdown, and level of independence in activities of daily living at admission to rehabilitation as measured by the Barthel Index (Bouwstra et al., 2019).

The following questionnaires were administered in-person at readmission to the rehabilitation service to characterize psychological and physical well-being and their association with participation to telerehabilitation:

- Cognitive Reserve Index questionnaire (CRIq) evaluates the cognitive reserve of an individual by means of the compilation of information relating to their entire adult life (Nucci et al., 2012)
- General Self-Efficacy Scale (GSE) evaluates a general sense of perceived self-efficacy with the aim to predict coping with daily frustrations as well as adaptation after experiencing all types of stressful life events (Schwarzer & Jerusalem, 1995)
- Connor and Davidson Resilience Scale (CD-RISC) is a unidimensional self-report scale that measures resilience or how well one is equipped to bounce back after stressful events, tragedy, or trauma (Campbell-Sills & Stein, 2007)
- 12-Item Short Form Survey (SF-12) is a self-reported outcome measure assessing the impact of health on an individual's everyday life (Ware Jr et al., 1996)
- Patient Health Questionnaire (PHQ-9) consists of nine items and assesses different depressive symptoms (Kroenke et al., 2001)
- Beck Anxiety Inventory (BAI) measures the severity of anxiety (Ulusoy et al., 1998)

Telerehabilitation program

Beginning on March 16, 2020, each patient was contacted by phone. An offer was made to restart their COVID-19 interrupted rehabilitation program through teleconsultations with a specialized physiotherapist and a medical doctor. The telerehabilitation program aimed to deliver real-time clinical information and physiotherapy services 2-3 times/week according to individual needs during the COVID-19 lockdown; each session lasted approximately an hour. By appointment, an expert physiotherapist contacted the patients by video call at a pre-arranged time to deliver customized exercises. Safety was guaranteed by the physiotherapist's continuous monitoring. The patient could follow verbal prompts and live demonstrations by the physiotherapist, who could correct any mistakes or address any questions and concerns in real-time and share on the screen helpful documents and images. The physiatrist was available in case of specific requests from the client (e.g., pain, drug therapy, etc.). Skype, a free software program owned by Microsoft that allows for free voice and video calls one-to-one or as a group, instant messages, and the sharing files with other people, was employed (Armfield et al., 2015). Skype can be used on a mobile phone, computer, or tablet. The authentication of participants was done at the beginning of every session to ensure the patient's privacy.

Feasibility and acceptability assessments

Evaluations of feasibility and acceptability were made at the end of the telerehabilitation program. We defined acceptability as satisfaction with the telerehabilitation program, the perceived strengths and weaknesses of the intervention, and the reasons for non-participation. Feasibility included the rate of participation in the telerehabilitation program, the adherence to the intervention, and familiarity with the technology.

Acceptability

The researchers developed a survey with a list of barriers and facilitators to telerehabilitation to evaluate the acceptability of the telerehabilitation intervention. Participants rated items on a 5-point Likert scale, ranging from 1 (strongly agree) to 5 (strongly disagree). To identify possible obstacles to the completion of this intervention, a list of possible reasons was provided to the patients who did not complete the program, to rate.

Feasibility

Feasibility was assessed as the rate of participation and adherence to the telerehabilitation program as measured by the percentage of sessions lost, withdrawal, and dropout rate. The System Usability Scale (SUS) was administered to test the usability (Bangor et al., 2008). The Technology Familiarity Scale (TFS) was administered to measure everyday technology in older people and people with a disability (Crotty et al., 2014).

Statistical analysis

All continuous variables were expressed as mean ± standard deviation. Between-group differences among patients who either received telerehabilitation or did not, were explored with the Wilcoxon rank-sum test. Correlations between clinical, demographic, and psychological variables and participation/non-participation in the telerehabilitation program or familiarity of technology were tested with the Spearman-Rho test. Finally, a logistic regression analysis was performed including those variables that correlated significantly with the participation in the telerehabilitation program (dependent variable); and a linear regression model was used to underline variables that predicted the familiarity to technology (dependent variable). Statistical significance was set at a level of $p<0.05$. Statistical analysis was performed using STATA 13.1 software.

5.3 Results

Clinical and demographic characteristics of the participant sample

The telerehabilitation program was proposed to 33 patients who were receiving motor rehabilitation that was interrupted by the COVID-19 lockdown: among them 23 patients were enrolled in the study (57.3±13.3 years, 10 males and 13 females), and 10 patients were excluded (8 patients refused to participate, 1 was a child, 1 had severe cognitive impairments). Eleven of the 23 patients (49.09 ±10.7 years; 4 males and 7 females) took part in the telerehabilitation program. The clinical and demographic characteristics of the two groups are summarized in *Table 1*.

Table 1. Clinical and Demographic Characteristics of the Participant Sample

	Mean (SD)			*p* value
	Telerehabilitation program (N=11)	No-Telerehabilitation (N=12)	Total (N=23)	
Age (years)	49.09 (10.72)	64.91 (10.94)	57.34 (13.32)	0.004
Sex (M/F)	4/7	6/6	10/13	0.510
Barthel Index at admission	76 (15.59)	87.27 (15.71)	81.90 (16.31)	0.054
Living situation (detached house/ apartment)	3/5	3/6	6/11	0.858
Diagnosis (neurological disability/orthopedic disability)	4/7	8/4	12/11	0.146
Time from the damage to the COVID-19 pandemic (< 6 month /> 6 month)	7/3	5/5	12/8	0.361
Live alone / Presence of a caregiver	2/8	3/8	5/16	0.696
Employment (not work / work)	4/5	9/2	13/7	0.081
Cognitive Reserve Index, total	116.90 (17.84)	100.25 (13.72)	108.21 (17.64)	0.045

At the end of the COVID-19 lockdown (late May 2020), a set of outcome measures were collected to characterize the sample. All enrolled patients returned to in-person rehabilitation for conventional therapy. The group that took part in the telerehabilitation program was not significantly different for clinical and demographic characteristics, except for age (p=0.004), CRIq score (p=0.04) and the performance in activities of daily living at admission to outpatient rehabilitation (p=0.05).

The number of falls at home (p=0.36) and the number of calls to the General Practitioner or other specialists (p=0.94) didnot differ between the groups; similarly, there was no significant difference in terms of familiarity with technology (p=0.13).

Descriptive analyses showed that all patients reported medium-high levels of resilience (28.6±9.4), high levels of generalized self-efficacy (29.9±8.1), medium levels of anxiety (8.3±5.9) and subthreshold depression (5.6±3.7). Physical (11.1±2.3) and mental self-perceived health (18.08±4.1) were similar across all samples. The psychological and physical profiles of the two groups are summarized in *Table 2*.

Table 2. The Psychological and Physical Well-being at Readmission to Rehabilitation

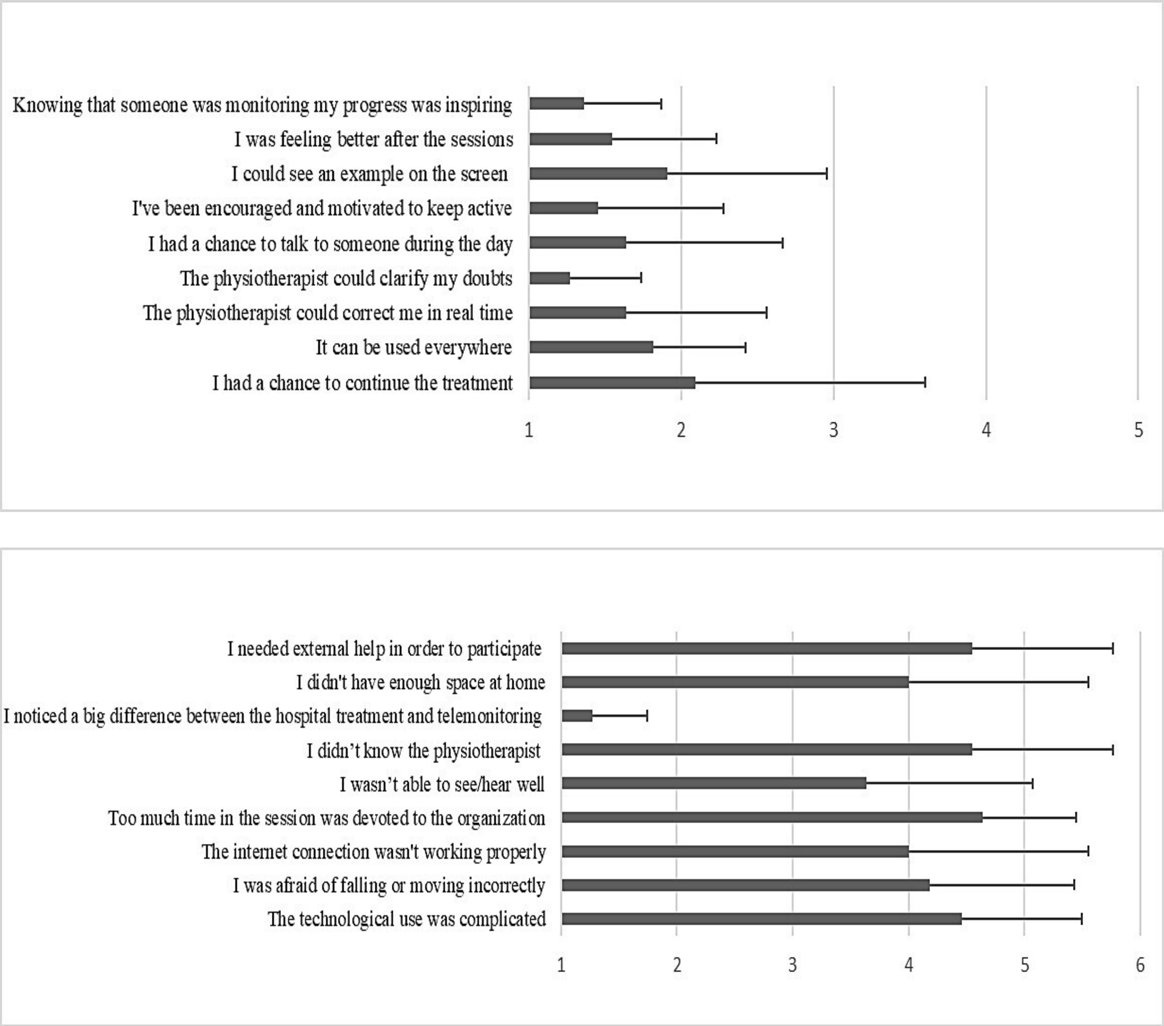
	Mean (SD)			*p* value
	Telerehabilitation program (N=11)	No-Telerehabilitation (N=12)	Total (N=23)	
PHQ9	5.09 (3.26)	6.16 (4.21)	5.65 (3.74)	0.599
BAI	7.09 (5.61)	9.5 (6.33)	8.34 (5.98)	0.323
GSE	31.81 (5.43)	28.09 (10.17)	29.95 (8.18)	0.448
CD-RISC10	31.63 (8.81)	25.91 (9.61)	28.65 (9.48)	0.280
TFS	26.54 (4.94)	22.66 (7.77)	24.52 (6.72)	0.138
SF-12 PCS	11.45 (2.84)	10.83 (1.89)	11.13 (2.36)	0.489
SF-12 MCS	18.18 (4.66)	18 (3.76)	18.08 (4.12)	0.852

* PHQ9, Patient Health Questionnaire; BAI, Beck Anxiety Inventory; GSE, General Self-Efficacy Scale; CD-RISC 10, Connor And Davidson Resilience Scale; TFS, Technology Familiarity Scale; SF-12 PCS, 12-Item Short Form Survey Physical Component Summary; SF-12 MCS, 12-Item Short Form Survey Mental Component Summary

Feasibility and acceptability

The overall adherence to the program was high; only one participant missed almost 30% of the sessions due to technical issues. No participants dropped out or withdrew during the program.
The group of patients who participated in telerehabilitation reported that the most relevant perceived limitation was the difference between the conventional treatment and telerehabilitation. However, they described the program as beneficial and satisfactory because the physiotherapist could address their questions. They also found it useful knowing that a clinician had monitored their progress; they were therefore encouraged and motivated to stay active. See *Figure 1.*

Figure 1. Self-reported Advantages and Disadvantages of Telerehabilitation Program



The patients who took part in the telerehabilitation program reported a good perception of usability as assessed by the SUS (78.6±14.1). The patients who did not take part in telerehabilitation reported their reasons for refusing the treatment were: their perception that the treatment was not useful (n=4); the lack of a suitable Internet connection (n=4); and their inability to use a computer or any other device with an Internet connection (n=4).

Predictors of participation in telerehabilitation and familiarity of technology

The telerehabilitation program was positively associated with CRIq (rho=0.4427, p=.0506) and negatively associated with age (rho = –0.6248, p = .003) and BI score (rho = –0.5658, p = .009). In the adjusted multiple logistic regression model, age (p=.017) and CRIq score (p=.043) remained a significant predictor for taking part in the telerehabilitation program, contrary to BI (.127). See *Table 3*. Furthermore, age was negatively correlated with resilience (rho=-0.5722 p=.008).

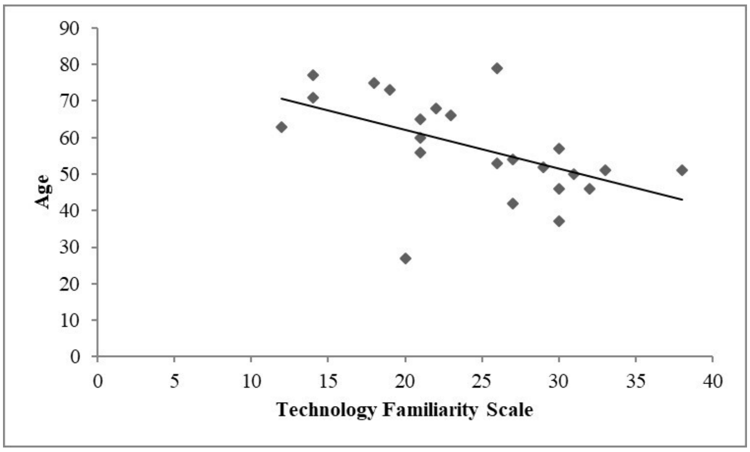
Table 3. Logistic Regression Analysis for Telerehabilitation

Variable	Coefficients		95.0 % Confidence interval		z	Significance
	Beta	Std.error	Lower	Upper		
Age	.865	.052	.769	.974	-2.38	.017
CRIq tot	1.076	.039	1.002	1.15	2.02	.043
BI	.951	.030	.893	1.01	-1.53	.127

* CRIq, Cognitive Reserve Index; BI, Barthel Index

TFS score was positively associated with CRIq score (rho=0.4590, p=.0418) and negatively associated with age (rho=- 0.5604, p=.0102) and the number of calls to the General Practitioner or other specialists (rho=0.4802, p=.0321). TFS score was positively associated with GSE score (rho=0.5032, p=.0237) and CD-RISC score (rho=0.5146, p=.0203). TFS score was positively associated with SF-12 PCS score (rho=0.4403, p=.0520) and negatively associated with BAI score (rho=-0.5275, p=.0168). In the adjusted linear regression model, age (p=.009) and CDRISC score (p=.032) remained a significant predictor to familiarity with technology. See *Figure 2* and *Table 4*.

Figure 2. Impact of Age and Resilience on Technology Familiarity



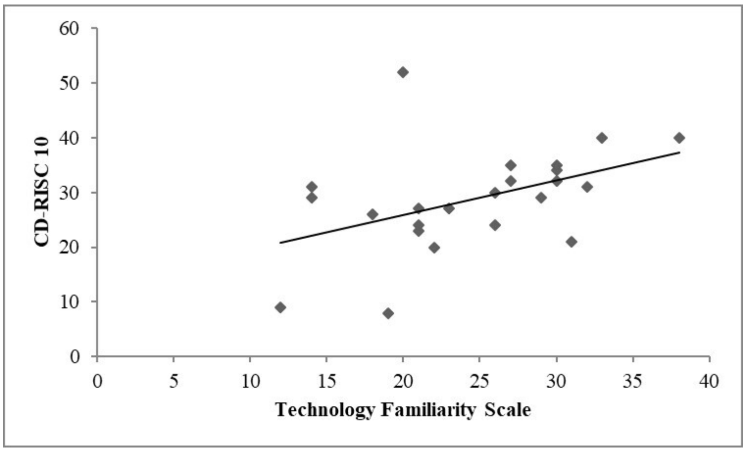


Table 4. Linear Regression Analysis for Familiarity of Technology

Variable	Coefficients		95.0 % Confidence interval		t-value	Significance
	Beta	Std.error	Lower	Upper		
Age	-.268	.093	-.462	-.074	-2.88	.009
CD-RISC	.318	.138	.030	.605	2.30	.032
BAI	-.452	.224	-.919	.013	-2.02	.057
CRIq tot	.133	.077	-.028	.295	1.71	.101
GSE	.291	.171	-.067	.649	1.69	.106

* CD-RISC 10, Connor and Davidson Resilience Scale; BAI, Beck Anxiety Inventory; CRIq, CognitiveReserve Index; GSE, General Self-Efficacy Scale.

5.4 Discussion

During a pandemic, specific actions should be taken to ensure that persons with physical disabilities have equal access to information, health care services, and the support they need to stay healthy and safe. Digital practices offer a safe alternative service delivery model to traditional in-person treatment.

However, some researchers questioned whether physiotherapists were ready to introduce digital practice to provide rehabilitation services during the COVID-19 pandemic period (Dantas et al., 2020). Italy, as is the case for many countries worldwide is in need of additional laws and practical guidelines on how to engage in digital practice, so that required competencies and responsibilities are clearly stated.

The aims of our intervention were to ensure the continuity of rehabilitation while respecting social distancing; to deliver individualized programs to prevent secondary complications; and to maintain the greatest degree of patient autonomy (Boldrini et al., 2020b). Specifically, the study evaluated the feasibility and acceptability of a telerehabilitation program for adults with physical disabilities.

Though Skype is one of the most popular software applications to facilitate video communication (Armfield et al., 2012), little is known about its technical adequacy for telemedicine (Mantokoudis et al., 2013; Bruyneel et al., 2013). Many studies have questioned the advisability of employing the non-subscription version of Skype for clinical purposes, due to its unknown capacity to protect privacy and security. Concerns about the security and privacy of Skype are likely to be a significant barrier to its further uptake in some jurisdictions (Armfield et al., 2012). In our study, sufficient risk-reducing measures were implemented, and no violations were reported regarding privacy, confidentiality, or security.

The patients who participated in telerehabilitation reported a favorable perception of the program's usability. After receiving training, they did not find the technology to be complex and they became comfortable with its use. They also suggested that future users would also quickly adapt to the technology.

Despite these positive reports, the patients who took advantage of telerehabilitation preferred the traditional in-person treatment. They perceived a difference between the in-person hospital and remote treatments in terms of quality of service. Similarly, Cranen et al. (2011) reported that patients with chronic pain were concerned with the lack of therapist in-person contact on their ability to successfully participate in an exercise program, while appreciating the flexibility that telerehabilitation could provide.

There was good adherence to the telerehabilitation program in the current study. All participants completed the intervention and only one patient failed to completely participate due to technical problems related to the Internet connection. Patients described the program as beneficial for the following reasons: the physiotherapist could address patient concerns; knowing that someone monitored the improvement of patients was inspiring; and patients were encouraged and motivated to stay active. Satisfaction with the telerehabilitation was reported as high in two prior studies that compared the satisfaction between telerehabilitation and in-person therapy in stroke patients (Cramer et al., 2019; Piron et al., 2008). Given the overall high levels of satisfaction and the few technical barriers encountered, we can conclude that the telerehabilitation intervention had high acceptability.

Patients who opted not to take part in telerehabilitation reported the most relevant reasons for their treatment refusal were the perception that the treatment was not useful; the lack of a suitable Internet connection; and their inability to use a computer or other devices.

Hamilton et al. (2018) suggested that providers need to systematically support telerehabilitation technology use in their patients. This includes providing positive initial experiences; verbal support during instruction and feedback about performance; support to handle the cognitive demands of using technology; educational support to assist with learning; and motivational and emotional support.

In the current study, familiarity with technology was related to age and resilience; participation with telerehabilitation was associated with younger ages and higher cognitive reserves. Older participants reported lower levels of familiarity with technology than younger people. A possible explanation for this finding is that younger people have had more experience using technology than older people (Bandura et al., 1999). Several large-scale studies found that older adults do not use certain technologies to the extent that younger adults do (Adler, 2006; Madden & Fox, 2006) and suggested that older adults are unable, unwilling, or afraid to use technology.

Familiarity with technology was related to resilience, defined as the ability to readily adapt or recover following change or adversity (Wagnild & Collins, 2009). A person with high level of resilience is able to adapt to new life experiences, restore their balance when faced with difficult situations, and avoid the potentially detrimental consequences of stress. During the pandemic, patients with physical disabilities were forced to newly negotiate their relationships with healthcare providers of telerehabilitation and adapt to previously unfamiliar technologies.

Czaja et al. (2006) found two main personal barriers to technology adoption in the elderly: low self-efficacy and high anxiety regarding computer use. Enhanced training and education may therefore be necessary to inform older users about the benefits of technology use (Czaja et al., 2006). Moreover, prior studies demonstrated a relationship between self-efficacy and technology use and identified issues affecting technology acceptance in older persons and persons with disabilities (Melenhorst et al., 2006; Ziefle & Wilkowska, 2010).

The current findings suggested that both age and cognitive reserve, defined as the set of learning and cognitively stimulating activities acquired by the individual during his life, were uniquely predictive of participation in the telerehabilitation program. Cognitive reserve was evaluated with the CRIq which takes into consideration education, work, and recreational experiences. CRIq is useful to quantify social, cultural, cognitive, and human capital (Nucci et al., 2012). A positive correlation was found between agreement to engage with telerehabilitation and higher cognitive reserve.

Both anxiety and depression had been proposed by Choi et al. (2013) as potential factors influencing Internet use in older adults. The current study, however, did not find a clear relationship between psychological status, physical well-being, and the adoption of the telerehabilitation technology, even though all patients reported medium levels of anxiety and subthreshold depression. Participants in our sample presented with disabilities that were associated with higher levels of anxiety and depression in a prior study (Brenes et al., 2008). Such symptoms can contribute to psychological and physical dysfunction beyond the effects of disability itself with detrimental effects on quality of life (Mitchell et al., 2006).

This study had several limitations. First, the small sample size limited the significance of the results. However, our sample was unique in that it included a cohort for which outpatient rehabilitation was interrupted during the COVID-19 lockdown. Second, to guarantee the continuity of care during the pandemic, the telerehabilitation program was rapidly implemented with variable training, but without a specific training protocol. Third, the research findings were limited by the cross-sectional design that did not allow for the detection of pre-post variations of selected outcomes. Fourth, information regarding the use of technology was self-reported and digital proficiency was not directly assessed. Lastly, cognitive impairment was an exclusion criteria in this study, limiting the generalizability of the results to adults with cognitive disabilities.

5.5 Conclusions

During the COVID-19 lockdown that ceased in-person rehabilitation services, a telerehabilitation program was an adoptable solution, albeit with some associated barriers. While there was good adherence to the telerehabilitation program, and overall positive perceptions of its acceptability and effectiveness, patients preferred “in-person” services.

Several barriers were highlighted. This study showed that younger age and good cognitive reserve can be considered favorable personal characteristics for participation in a telerehabilitation program, whereas resilience and age were more generally associated with familiarity with the technology.

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GENERAL DISCUSSION

1. SUMMARY OF FINDINGS

During this thesis work, I explored the potential benefits of plasticity-based technologies and interventions in a clinical rehabilitation setting, considering both motor outcomes - psychological health and cognitive functioning. It was possible through the application of multidisciplinary approach that comprehends medical practioners, physiotherapist and neuropsychologist.

In our studies, the condition of the stroke and multiple sclerosis (MS) patients was evaluated under various aspects such as physical, psychological, cognitive, and social aspects to capture as many dependencies as possible and, as a consequence, to be able to understand the underlying reasons for poorly effective rehabilitation.

In many studies, when evaluating the effects of post-stroke rehabilitation, researchers focus their attention mainly on the assessment of motor and functional ability deficits (Cordun & Marinescu, 2014; Muellbacher et al., 2002). Moreover, motor, and cognitive impairments were commonly examined independently of each other. However, research of simultaneous performance of motor and cognitive tasks has identified an interaction between them. Cognitive-motor interference is common in various clinical populations, among these stroke (Plummer et al., 2013) and MS (Leone et al., 2015). Given the significant impact of cognitive deficits on the everyday lives and overall QoL of persons with neurological condition, it is imperative that we develop and validate mechanisms for effectively treating cognitive dysfunction.

The main reason to involve neuropsychologists in rehabilitation settings, is in terms of caring for patients with brain-related disorders, like behavioural, cognitive, and emotional difficulties that are frequently present in this population, and to describe brain-behaviour relationship. In general, the neuropsychological assessment in a rehabilitation setting aims: to identify cognitive and behavioral strengths and weaknesses, to assess for the presence of emotional issues that require intervention, to help in treatment and discharge's planning, understanding barriers to rehabilitation engagement and providing strategies for improvement it, educating the patient and his family of the disability consequences, and offering strategies to compensate them. It would be considered that the evaluation should be repeated over time because patients almost always improve over time, besides the fact that, in a specific time point, the patients may have several sensory, perceptual, and motor impairments that constrain their ability to do some neuropsychology evaluation (Johnson-Greene, 2018).

The literature provides considerable evidence that the presence of cognitive disorders or mood disorder besides influencing each other's may greatly impair the process of rehabilitation and affect its final outcome in stroke and multiple sclerosis patients (Rickards, 2005; Feinstein, 2006; Szczepanska-Gieracha et al., 2010; Ahn et al., 2015; Park et al., 2015; Gill et al., 2019). Moreover, to properly evaluate the effects of treatment, one must also consider the mental state of the patient. Substantial evidence shows that anxiety, depression and the two in comorbidity are associated with higher levels of disability (Brenes et al., 2008). These "secondary conditions" contribute to psychological and physical dysfunction beyond the effects of the disability itself and represent significant barriers to general quality of life (Mitchell et al., 2006). Poor efficacy of physiotherapy is related to the presence of depression symptoms, a low level of acceptance of illness and a lack of a sense of self-efficacy in the rehabilitation process (Kobylańska et al., 2018). In addition, also the social support is an important factor: adults with physical disabilities may have fewer opportunities of favourable exchange with one's proximal social environment, which has positive effects on both mental health and wellbeing (Avendano & Berkman, 2014).

Therefore, it would be useful to consider more the International Classification of Functioning, Disability and Health (ICF), a useful tool for multidisciplinary approach, which can promote the communication and collaboration in the healthcare team. In this way, neurorehabilitation could focus on comprehensive assessment and rehabilitation with biopsychosocial approach.

Basic neuroscience studies provided evidence that the human brain is able to change and modulate itself according to external experiences and behaviours, leading to physiological and anatomical changes, such as a functional reorganization of cortical sensorimotor network (Sharma et al., 2013). Cortical reorganisation after brain injury is facilitated by early, intensive, repetitive training and it is an optimal strategy to promote recover from impairment (Coleman et al., 2017). However, during early stages of rehabilitation, more probably, the patient is often in a condition of poor mobility; for this reason, an alternative intervention that use also cognitive processes is to be consider. Since each patient's motor and cognitive strategies and degree of improvement are extremely different from each other and depend closely on multiple factors such as the type and site of injury, the degree of impairment, and the time elapsed between the event and the start of treatment, patient tailor-made therapies are always the most appropriate; since they also take into account the psychological characteristics, the intrinsic motivation and the level of engagement treatment.

Knowledge of the factors responsible for the poor efficacy of rehabilitation may facilitate an individual approach for each patient and enable the prompt set-up of the necessary therapeutic support for those whose rehabilitation process might be at risk of failure. Therefore, comprehensive neurological rehabilitation, considering the mental health problems and socio-economic circumstances, is essential to achieve high efficacy of physiotherapy. For these reasons we suggest that all individuals should receive a more comprehensive neuropsychological assessment to gain a greater understanding into emotional and cognitive strengths and weaknesses, and if necessary, the possibility to start comprehensive rehabilitation that consequently influence the outcome.

Even if the effectiveness of various types of rehabilitative technologies has been proved and they not present adverse effects, their clinical use both in stroke and MS is still poor. You should consider that the available technology cannot completely replace the adaptability and skills of the healthcare practioner; complete replacement of the therapist is not a viable route because it could lead to the failure of the use of technology for rehabilitation purposes. There are still several obstacles that slow down the introduction of technological advances in daily clinical practice, among these, communication biases between producers and potential adopters, and their high costs imposes due the rapid and constant development of technological tools that prevents the implementation of a sufficient amount of testing on their effectiveness. Technologies devices must in fact be understood as a new tool in the hands of the therapist who can apply it only where he believes that the patient can benefit from it.

I discussed preliminary results on the effects of combined cerebellar TDCS with intense task-specific intervention, which is Task-Oriented Circuit Training (TOCT) in people who suffered from MS, both on motor impairments (gait, balance, and mobility), psychological status and executive function abilities. Despite cerebellar activity modulation might play an essential role in developing potential rehabilitation strategies in MS, our main finding revealed that TOCT effectively ameliorates balance and mobility, but cerebellar tDCS doesn't boost motor training effects; the latter may only boost the effects of motor training on the perceived quality of life. It is known that the cerebellum plays a crucial role on balance and motor control, integrating primary motor cortex activity through specific pathways (Grimaldi et al., 2016); it is also activated in adaptive motor learning circuits (Celnik, 2015). Our result perhaps depends on the residual functional reserve of the cerebellum, i.e., the cerebellum’s capacity to compensate for pathology and restoration, on which the effects of this approach depend. The cerebellar reserve is progressively lost while cerebellar damage progresses, affecting motor, cognitive, and affective control. To increase that reserve, the neuromodulation strategies as motor and cognitive rehabilitation and non-invasive cerebellar stimulation are considered. It is therefore desirable define the best patient-tailored stimulation protocol (Billeri & Naro, 2021; Bordignon et al., 2021).

Furthermore, a more general explanation in terms of stimulation, is in the choice of specific treatment protocol, that considers the appropriate temporal and spatial relationship between the combined treatments, as both motor training and brain stimulation seem to promote neuroplasticity changes in the human cortex, but their combination may diminish the effects of the single treatment on motor outcome. Cabral et al. (2015) suggest that tDCS performed before (not during or after) encourages optimization of motor training-induced plasticity. About executive functioning, the two groups did not differ on measures of response inhibition, neither for accuracy nor for reaction times. This result is in line with Mannarelli et al. (2020) that demonstrated the role of the cerebellum in executive attentional functioning, particularly in inhibitory control. It could be that the improvements in cognitive function may depend, at least partially, on the enhanced motor function and a better cognitive resource allocation (Pope & Miall, 2012). Despite having been recognized the effects of stimulation and physical activity in a variety of psychiatric diseases (Kuo et al., 2017), in our sample, anxiety and depression symptomatology was not show modifications, although patients perceived a better mental HRQoL after the treatment. The role of the cerebellum in cognitive functioning and emotions has traditionally received little attention, probably because it has always been mainly associated with motor functions. However, it has been shown that there is a close network of neural connections with reciprocal feed-forward and feed-back between the cerebellum and areas of the cerebral cortex connected with higher-order behaviours (Koziol et al., 2014). Although positive effects on mobility and inhibition control ability, as well as the absence of adverse effects following the combined treatment, this pilot study cannot draw definitive conclusions. Moreover, given the analogies and close connections described above, the role of cognitive reserve in cerebellar functioning is to better understand its potential protective role.

There is significant neuroplasticity of cognitive functions in individuals with MS. To maintain cognitive functioning, occurring the homologous region adaptation, local activation expansion, and extra-region recruitment. A great of this neuroplasticity is adaptive, but in many situations may be maladaptive, especially in individuals with disease progression and significant cognitive impairment. However, such neuroplasticity can be induced through neuropsychological rehabilitation, to "normalize" brain function and behavioural output (Chiaravalloti et al., 2015).

Another study in multiple sclerosis was carried out, again considering the concurring between the motor and cognitive systems in neurorehabilitation. Again, it is necessary to consider not only motor dysfunctions but also the major cognitive dysfunctions in MS patients as cognitive processing speed, attention/concentration, and executive functioning (Giazkoulidou et al., 2019). In MS patient, the ability of doing a motor task simultaneously to a cognitive one is frequently affected (Ghai et al., 2017) and resulting in cognitive–motor interference and operationalized as dual task costs (Sosnoff et al., 2017). It is probable that motor deficits enhance the cognitive demands necessary to execute functional movements, and the concurrent performance of tasks may exceed cognitive processing abilities.

I presented a study protocol for a randomised controlled trial with the aim to test the efficacy of commercially available Video Game Therapy (VGT) on mobility and dual tasking in people with MS compared with standardised balance platform training. Our expectancy from the proposed investigation is to detect a more significant effect on mobility, balance and dual tasking through VGT compared with a conventional approach. It is well known that conventional rehabilitation approaches are often repetitive and boring, decreasing patient's interest and exercise participation. Patients' satisfaction represents one of the key features for treatment adherence and rehabilitation success also in MS patients (Jeong et al., 2019); for this to happen it was important to identify some treatment that engaged the patient. Among these, the exergaming in which individual with MS defined the gaming experience as fun, challenging and self-motivating, all critical elements for a successful motor learning (Forsberg et al., 2015). Active video games not only engage patients in motor activities, but it simultaneously requires subjects to use cognitive abilities (as attention and alertness) for managing inputs into an enriched environment (Prosperini et al., 2013). Active video games' multisensory feedback provided to patients may potentiate the use-dependent plasticity processes in the sensorimotor cortex, promoting functional recovery (Maggio et al., 2019). Furthermore, combined training of cognitive and motor abilities in constantly changing virtual environments is particularly suited to address dual tasking as required for the constantly changing situations of everyday life (Schaeffer et al., 2019). Patients with multiple sclerosis are often afflict by the unpredictability of their illness and have to struggle with sudden life changes. This condition can conduct to perceived lack of control, high levels of stress, anxiety, and depression. Anxiety and depression represent an important role in patient' perceived health and well-being, which thus impacts the symptoms' severity and overall quality of life. Patients' psychological status can influence the liability toward rehabilitation treatment; therefore, the psychological counselling should be provided during the rehabilitation treatment to achieve a successful patients' care. Therefore, it must be considered fundamental the early identification of psychological disturbances as to identify potential solutions to mitigate its effects, for example, the social support appear to mitigate the impact of anxiety and depression (Hanna & Strober, 2020). Finally, we expect to observe greater modifications on motor, cognitive and psychological evaluation of people who received rehabilitation through video game platforms.

The importance of integrated rehabilitation of cognitive and motor processes should also be emphasized in Stroke population; although attention can affect upper limb motor recovery, in most rehabilitation interventions, it is not taken into consideration. In addition, the same importance is given to role of engagement in stroke survivors rehabilitation.

Among cognitive deficits, attention deficit is the most typical in stroke patients; it appears as diminished concentration, distractibility, reduced error control, and reduced multitasking capabilities, mental slowness, and mental fatigability (Loetscher et al., 2019). It was identified a probable causal relationship between attention deficits and poor functional recovery in stroke patients, maybe, attention is a prerequisite for learning, and inability to assist may prevent re-learning of movements, thus impeding recovery (Hyndman et al., 2008).

In this dissertation, I therefore discussed the results of a study that aimed to define the role of attention and engagement in motor recovery in a sample of patients with subacute stroke who underwent a novelty rehabilitation strategy: Action Observation Training (AOT). It is a training based on mirror neuron system (MNS) which commonly includes action observation and action execution of goal-directed daily actions (Zhang et al., 2018). Directing visual attention explicitly during action observation training facilitates corticospinal excitability of the injured sensorimotor system in the primary motor cortex and may quicken motor re-learning through observation (D'Innocenzo et al., 2017). By studying the clinical effects of the AOT in stroke patients, it was demonstrated that activation of the MNS by AOT positively impact not only motor but also cognitive recovery (i.e., concentration and mental multitasking) (Mao et al., 2020), emerging again the relationship between the motor and cognitive systems. AOT in rehabilitation may have top-down effects concerning higher-level networks that influence peripheral circuits, for example, motor areas, central movement planning areas, and peripheral structures (Mulder, 2007).

All patients improved motor function; however, the group without attention deficit reported a more significant gain. It was emerged that also stroke severity and anxious and depressive signs/symptoms are significant predictor for increment of FMA total score. This is in line with previous research: mood disorders (e.g. depression, anxiety, apathy) are often observed in stroke patients and could produce a significant degree of psychological distress influencing quality of life; moreover, exhibiting a negative impact on functional recovery associated with various physical disorders and cognitive dysfunction (Chemerinski et al., 2000; Hama et al., 2020).

Patients with attention deficit described a lower level of engagement and a lower mean accuracy, tested through the performance of interactive computerized exercises used as an approach to maintain concentration during the training. Regarding the accuracy, the trend showed sustained improvement up to the third week and decayed at the last week of treatment; maybe due to a decrease in involvement of the training that could became boring and less stimulating. In our sample, mean engagement score was a potential predictor to mean accuracy score, and the presence of attention deficit a potential predictor of engagement. These results are in line with the literature; stroke rehabilitation seems to be most efficacious when therapists encourage patients' active participation and engagement, which, in turn, is determined by their emotional status and cognitive functioning (Lequerica et al., 2009); indeed, a raised patient's engagement seems related to greater attention during exercise (Danzl et al., 2012). Mao and colleagues (2020) notice that patients with attention deficit have difficulty in understanding and collaborating with the therapist, resulting in a poor rehabilitation outcome. In our sample, the attention deficit group described the AOT as less motivating and stimulating and perceived a minor sense of accomplishment and gratification; reported major difficulties in focusing and in being absorbed in the task declaring it more mentally demanding and describe the duration of daily session less adequate. They perceived the training less fun, energising, and less pleasurable and not interesting to be repeated at home.

In stroke patients, but in general in patients with chronic diseases, therefore also MS, it is essential to maintain a certain continuity in the treatment over time, both for the functional motor area but also for the neuropsychological and social one. To date, a comprehensive view of QoL has been recognized including physical and psychological health, social relationships, and environmental quality (World Health Organization, 1996). Generally, rehabilitation intervention focusses on the first three months after stroke onset (Ekstam et al., 2007; Bergström et al., 2011; Lui & Nguyen, 2018), subsequently the patients are abandoned; we underestimate the impact of stroke in the long term, even considering the social and economic implications of its sequelae in society. Rehabilitation has to meet personal needs and expectations to improve the quality of life over time and information about the perceived impact of a stroke may help individualizing the rehabilitation provided. It would be necessary to take multidisciplinary care of patient even years after the acute event and better manage the patient in the community. For better understanding how stroke affects disability and health-related Quality of Life (HR-QoL), in this thesis, I have discussed how these parameters change in relation to time and type of treatment through a specific disease self-report questionnaire: the Stroke Impact Scale (SIS). Furthermore, it was identified demographic and clinical factors at baseline that influence disability and HR-QoL at the end of treatment and at six months follow-up.

During rehabilitation and up to six months, there is an overall improvement in disability and HR-QoL except for Memory and Thinking Ability, Emotions and Communication domains, without any significant differences between rehabilitation protocols, specifically the robot-assisted therapy combined with hand functional electrical stimulation and intensive conventional therapy, as previously reported in other studies (Conroy et al., 2019; Ahmad et al., 2019). Perhaps, the rehabilitation process, regardless of its type, is perceived as a vital process for "returning" the previous life and as a process that has enabled and sustained adaptation to change to meet the needs of new circumstances. Determination, pushing limits, and recognition of progress are vital factors influencing self-efficacy, also thanks to experiences through contact with other patients.

Conversely, it was a deterioration at a long-term follow-up, which is 6 years later, with a more marked worsening in the physical domains, the same for which there was a more significant increase in the 6 months follow-up. Thus, there is an improvement during rehabilitation, and then occur progressive deconditioning; this underlines the common problem of lack of movement and physical activity in the chronic patient and learned disuse (Han et al., 2017). The same results emerge from other studies that used the SIS and carried out the follow-up over the time (Lai et al., 2002, 2003; Coral et al., 2008; Susanne et al., 2012). On the contrary, Memory and Thinking, Emotions and Communication domains remain almost constant; despite the prominent ongoing physical invalidity, stroke survivors seem to adapt well psychologically to their disease (Hackett et al., 2000).

Emotion regulation is normally impaired following stroke, with implications for social participation and recovery (Cooper et al., 2015). In the initial months following a stroke, patients reported positive emotion, thus denoting adults' emotional resilience when faced with health defiance (Ostir et al., 2008). Although some stroke survivors experienced long-lasting incomplete acceptance of stroke, Smith et al. (2021) find a non-linear progression of experiences of post-stroke emotional adjustment, which fluctuate among positive and negative trajectories as result of trigger events. About these, social support, take stroke survivors to move along the positive path towards acceptance of stroke and their “new self”. Conversely, negative trigger as cessation of physiotherapy, could take patients from positive to negative trajectories. It was verified that functional capacity and social support are predictors of resilience of people with sequelae of stroke (de Lima et al., 2020). Thus, it is evident the need of raise awareness of healthcare professionals of “triggers,” in particular the interpersonal rapport practioner-patient.

In addition, in this study emerged that greater physical health perceived by the patient in the subacute phase is associated with a higher QoL in the months following the event; therefore, it would be possible to understand the needs and the real goal for improvement for each singular patient. Furthermore, it was found that individuals that receive outpatient rehabilitation experience less impairment and disability relative to inpatient up to 6 months; maybe patients experienced better recovery in familiar contests witch permit to generalize the restored functioning in ambulatory, moreover, improve mood and psychological well-being, perhaps due to family closeness or caregiver. Also, patient with somatosensory deficits experienced more disability and HR-QoL at 6 months’ follow-up; these influence and worsen physical outcomes and consequently social participation.

The same study also shows that patients with higher stroke severity, males and ≥ 65 years, experienced a higher impact of the illness in QoL at 6 years follow-up, revealing more difficulties in daily life; it could be possible that these categories of patients need major support with multidisciplinary approach.

The sex gap and its importance in post stroke recovery are not well defined; further studies are needed to fill this uncertainty (Wang & Langhammer, 2018). Relative to age, after years from the acute event, younger patients develop higher QoL; probably there is a reduction in self-efficacy and resilience that occur with advancing age (Salbach et al., 2006). It may be possible that younger, socially, and professionally active people, despite experiencing a deeper crisis, need less time than older people to regain their equilibrium.

In conclusion, although physical function deteriorates, quality of life in socio-emotional and cognitive domains stabilize during the years showing stroke patients capability to adapt to the new life condition. Nevertheless, the perceived general long-term impact after stroke highlights the importance to actuate adequate individualized rehabilitation even years after the acute event and of lasting care of the patient (Aziz, 2010), setting up community-based rehabilitative and vocational interventions with unique goal to maximize quality of life of patients. An aspect to be emphasized is that intervention must be encompasses not only physical activity but address all aspects of everyday life, including cognitive functioning, psychological well-being and social participation (e.g. working activity and social commitment).

COVID-19 pandemic, in particular way, alarm the field of rehabilitation medicine; indeed, the virus predominately affected frail and vulnerable individuals, that are persons with pre-existing chronic illnesses and physical disabilities (Bartolo et al., 2020; Boldrini et al., 2020a; Leocani et al., 2020). In addition, these patients suffered psychiatric distress ascribed to the spread of COVID-19 (Wang et al., 2020; Holmes et al., 2020). However, most of all, the coordinated multidisciplinary rehabilitation service has been interrupted or limited and the modalities of intervention have necessarily changed; this leaded pervasive anxiety (Boldrini et al., 2020b). Therefore, considering the COVID-19 pandemic era we are experiencing, there was a need to identify a remote intervention modality that contains the contagion and at the same time allows the patient to carry out rehabilitation, as have equal access to information, health care services, and professional support. This is the tele-rehabilitation, an off shoot of telemedicine that leverages telecommunication technologies to deliver rehabilitation services synchronously and/or asynchronously to patients at a distance.

Again, in this case, it is of primary importance to identify the variables that allow to obtain a good level of involvement and satisfaction in the treatment, albeit at a distance. Thus, in this thesis, the feasibility and acceptability of a telerehabilitation program, through Skype, in a sample of patients with physical disabilities have been studied. The barriers and facilitators to the adoption of telerehabilitation were identified and clinical, demographic, and psychological variables were analysed as predictors of success.

The telerehabilitation program was perceived as feasible, sufficient risk-reducing measures were implemented, and no violations were reported regarding privacy, confidentiality, or security. The program was well accepted by patients, despite some technology challenges; patients reported a favourable perception of the program's usability¸ they did not find the technology to be complex and they became comfortable with its use. Despite patients perceived differences in the quality of service and preferred traditional in-person treatment, there was overall high levels of satisfaction in telerehabilitation, patients described the program as beneficial because the physiotherapist could address their concerns; monitor the improvement and encourage and motivate to stay active. Patients who opted not to take part in telerehabilitation reported that the most relevant reasons for their treatment refusal were the perception that the treatment was not useful; their inability to use a computer or other devices and the lack of a suitable Internet connection. As reported by Hamilton et al. (2018), also in remote rehabilitation approach, is important that health providers engage their patients with the use of technology, assist them , give feedback about performance, and emotional and motivational support.

Concerning the predictors of satisfaction with telerehabilitation, age, resilience and cognitive reserve were identified. Relative to the age, younger people reported higher levels of familiarity with technology, perhaps due they have more experience using technology than older people; the latter are unwilling, or afraid to use technology, show low self-efficacy and high anxiety regarding computer use (Adler, 2006; Madden & Fox, 2006; Czaja et al., 2006), it follows that younger age is a favourable characteristic for participation in a telerehabilitation program. Familiarity with technology was also related to higher levels of resilience, during the pandemic, in fact patients with physical disabilities were forced to newly negotiate their relationships with healthcare providers and adapt to previously unfamiliar technologies. Moreover, it was found that patients with an higher cognitive reserve better agreed to engage with telerehabilitation; perhaps due the activities doing of these individual, in work or leisure time, that include more technologies device use. Finally, as we could expect, not only for the coexistence of the disability but also for the pandemic period, all patients reported medium levels of anxiety and subthreshold depression. However, this seems to not impact in the adoption of the telerehabilitation technology, nevertheless these are potential factors influencing Internet use (Choi & DiNitto, 2013).

In conclusion, digital practices offer an alternative service model to the traditional one that should be taken into consideration independently of pandemic era. Also in this study the physical, psychological and cognitive variables of the patient were considered together, in order to better understand their involvement in the remote rehabilitation approach and to adjust them. However, it remains to be set out adequate laws and practical guidelines on how to work with remote modality, as well as a staff and patient training and creation of adequate digital platforms with the help of professionals in the sector.

2. LIMITATIONS

We acknowledge that our experiments have some limitations, which can be improved by continuing these studies or in further studies. Firstly, it was used a small number of subjects; it would be useful to expand the sample. Secondly, data collection was carried out in part during the COVID-19 pandemic, which is a probable confounding factor in patients' response to the questionnaires administered. In general, it has negatively impacted various physical, psychological, and social aspects in the entire population, but pandemic stressor is likely to have an even greater impact on weaker groups, afflicted by previous fragility, as Stroke and MS populations. In addition, due to the state of emergency and contact with COVID-19 positive, treatments for some patients were suddenly stopped or is not possible doing the functional assessment pre- or post-intervention to verify the specific-treatment improvement. Then, to ensure the continuity of the assistance service during the pandemic, telerehabilitation was applied quickly without leaving the health workers the time necessary for an optimal implementation of the service and without carrying out appropriate training for remote consultations. Finally, at neurophysiological level, quantitative data were not acquired, meaning that it was not possible to evaluate if the treatment was able to generate changes at the level of cortical plasticity and facilitate functional improvement.

3. CONCLUSION AND FUTURE DIRECTIONS

The last decade saw impressive improvements in our understanding of the ability of the CNS to reorganize in response to changes in the environment and lesions, which ameliorate the comprehension into motor and cognitive mechanisms in Stroke and MS. Understanding of these neuroplasticity principles leads to the birth of more rational, hypothesis-driven strategies to promote functional recovery and, in general, to improve patient's care system.

Taken together, the studies presented in this thesis, demonstrate how considering mutual influences between cognition and action can provide exceptional research opportunities to enhance our understanding of adaptive human behaviours in real life. This dissertation highlights the relation between various cognitive processes and motor performance and raise several practical implications for designing effective motor training programs.

Thus, the importance of the neuropsychologist role emerges. Neuropsychological assessment aims to identify cognitive deficits that need to be rehabilitated to take advantage of the natural recovery curve and decreases the likelihood of maladaptive strategies or a reactive depression developing, consequent to feelings of helplessness and hopelessness. Furthermore, it helps to predict potential areas of difficulty for a patient that aims re-engage independence in normal activities of daily living (e.g., manage a family, return to work, resume school, driving, decisional and financial capacity, social integrations). Thanks to multidisciplinary approach, the neuropsychologist can use subjective assessment and behaviour observations obtained by other specialist, as speech or occupational therapists, to test hypothesis generated by cognitive test data (Bennett et al., 2001).

It is well known that patients with MS and Stroke, have decreased HRQoL, in part associated also with psychological profile. Prisnie et al. (2018), demonstrate that depending on the neurological condition, the two domains of quality of life (i.e., physical and mental component), show important connections with depression or anxiety witch delineate different manifestations. In particular, in MS patients, depression and anxiety has a sizeable correlation to both physical and mental components, although the contribution is greater for mental component. Regarding stroke patients, psychiatric symptoms may impede people regaining physical function, or alternatively, poor physical health may have especially negative implications for anxiety and depression. In conclusion, it is fundamental for the healthcare practioner to be aware of variables associated with quality of life, as anxiety and depression, to be able to treat them thus improving the lives of patients living with chronic diseases. Though psychological and neuropsychological consultation is utilizing in the rehabilitation setting, there is still low data concerning empirical support this service in rehabilitation populations (Prigatano & Pliskin, 2020). Various studies have demonstrated that cognitive interventions can significantly improve functioning in stroke and MS patients (O'Brien et al., 2008; Cicerone et al., 2011; Rosti-Ostajarvi & Hamalainen, 2014; Amato et al., 2013, 2014). Moving forward, a focus on identifying adaptive versus maladaptive neuroplasticity associated with specific cognitive rehabilitation programs would aid in the validation of the most effective cognitive rehabilitation interventions for patients with neurological condition.

In conclusion, translation of advances in translational neuroscience through clinical trials and into clinically useful treatments is critically slow. The development of standardized protocols and outcome measures, and a better interaction between clinicians and clinical and/or basic scientists must be encouraged, that is, it should be emphasis the advancing the interdisciplinary fields of neuroscience.

In neuroscience research, in the next future it should be better explored the mechanisms of neuroplasticity in motor recovery in specific training protocols that utilize technological devices. Then, define the optimal therapy dose, frequency, and time window to harness neuroplasticity mechanisms in damage brain. Moreover, it should be developed treatments with increasingly ecological properties and that allows a patients' active participation so from stimulate the cognitive system, thus integrate motor rehabilitation with cognitive rehabilitation. The data are still too heterogeneous to be able to establish standardized protocols and guidelines; thus, there is a need for more studies that includes neuropsychological, motor, and integrated technological aspects that allow the use of top-down approaches.

It should be good practice develop self-report questionnaires for patients relating to the level of satisfaction and engagement in the proposed treatment, in person or remotely, to bring out any critical issues, including the perception of effectiveness of the proposed treatment. Just as, it is important to evaluate the psychological variables capable of modulating or interfering with the commitment to treatment and its effectiveness, including resilience, self-efficacy, motivation, coping strategies, and in general, anxiety and mood disorders. Furthermore, is crucial investigate more the impact of the disease on the quality of life for several years from diagnosis, to identify which are the intrinsic and extrinsic factors capable of modulating the patient's perception of health and intervening on them. Depending on the level of disability of these patients, and therefore on the degree of independence, the caregiver's need for assistance plays a role of primary importance; therefore, collaboration with family members in the rehabilitation care should not be underestimated, especially if the final goal is telerehabilitation and consequently educational and emotional support for the caregiver.

The rehabilitation challenges related to COVID-19 are still present, so it would be useful continue to evaluate the material and economic resources available for the development of telerehabilitation and examination techniques that will allow remote dynamic testing. Remote rehabilitation requires not only specific audio / video communication platforms but also adequate health-care professional and patient training. Finally, the importance of guidelines that regulate the use of these domestic technologies in medical-care use is emphasized.

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