POLITECNICO DI MILANO
Department Of Electronics, Information and Bioengineering
Master of Science in Biomedical Engineering

Neuroengineering Compendium - Rehabilitation Robotics

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Chapter 1

Design experimental studies in rehabilitation

Progress in health care, an increase in levels of wealth, improvements in standards of living, and better nutrition, combined with reduced fertility rates, have contributed to an increase in the rate of older people over the population. According to recent projections, the number of Europeans aged 65+ will almost double over the next 50 years, from 85 million in 2008 to 151 million in 2060. There is a positive correlation between prevalence of neuro-motor diseases (e.g., stroke) and age. It led to an increased demand for novel and cost-effective solutions to improve the outcome of the rehabilitation process.

1.1 From research to decision making

The process that leads from research to decision making is characterized by 5 main steps:

1. Clinical evidence analysis: a systematic evaluation of evidence for a technology. This stage corresponds to evidence-based guidelines.

2. Outcome analysis: it consists of an estimation of the magnitude of the effects of a technology on the desired clinical outcomes (the benefits) and on potential harms (the risks). It determines if the benifit-risk ratio is sufficiently high to justify the technology.

3. Economic analysis: it corresponds to the analysis of the costs.

4. Cost-effectiveness analysis: the comparison between the clinical effects against the costs, to determine if the ratio is sufficiently high, to assure the sustainability

of the system

5. Ethical/legal analysis: analysis of the ethical and legal implications of the technology.

This methodological approach for medical devices prescription is quite novel, differently from drug regulation. The EU new regulatory for medical devices (EU Medical Device Regulation 745/2017, entering in full application next May 2021) has introduced as mandatory by the producer the evaluation of the effectiveness of the device for the defined clinical purpose. The adaptation to this new rules is still in progress. Beforehand, the certification of a medical device used to be determined by safety tests, and technological risk analysis, while the appropriateness used to be based on and experience-based evaluation of the single clinicians.

1.2 Evidence-based medicine

Evidence-based medicine (EBM) is defined as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" [1] (Fig. 1.1).

Figure 1.1: *Evidence-based medicine schema. Adapted from: Sackett DL, Rosenberg MC, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ. 1996;312: 71-72.*

This characterization highlights the three important parts of evidence-based medical practice:

- the patient,
- the evidence,
- the application of generalized evidence to the individual patient.

The evidence, by itself, does not make a decision for you, but it can help support the patient care process. The full integration of these three components into clinical decisions enhances the opportunity for optimal clinical outcomes and quality of life. This means that the role of the evidence is to support the clinician. Indeed, using evidence without an accurate evaluation based on the single patient's condition is to be avoided, according to EBM. As Sackett stated [1], EBM is the integration of best research evidence with clinical experience and patient evaluation.

Conceptually, evidence starts simply with what is observed. Every individual observation is an isolated piece of evidence. To generate higher quality evidence, however, it is important to compile, organize, and evaluate those individual observations in a systematic way (Fig. 1.2). Thus, an anecdotal observation constitutes evidence regarding a single event. A more organized compilation of several observed events can constitute a case series, a higher level of evidence. An even more organized way to evaluate an event or an intervention is to use systematic observation, as in an uncontrolled or controlled trial. A meta-analysis provides even higher quality evidence by systematically grouping together and synthesizing the results of multiple trials. The basic premise is that the more systematic the observations that are available (e.g., RCT instead of just a case series) the better the quality of evidence. Since EBM seeks to apply the "current best evidence" it is important to see for the highest quality studies that are available to address a given clinical question.

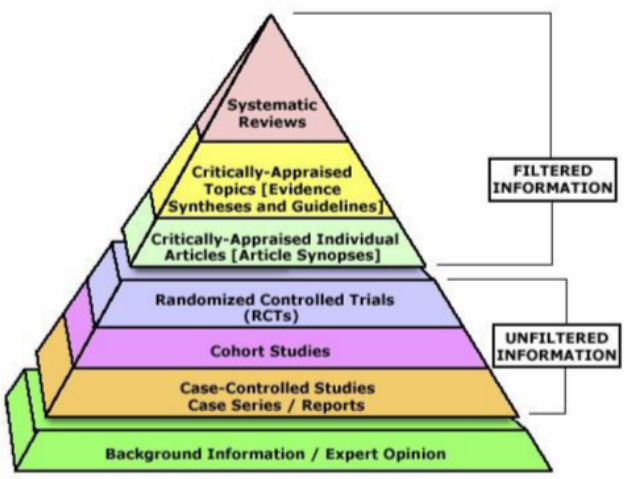

Figure 1.2: *Pyramid showing, top-to-bottom, the most important factors when making decisions in EBM. The choice must be led by systematic reviews, properly analysed, whereas personal experience and knowledge must be considered only when the literature does not provide enough information to rely on [1].*

1.3 Randomized Controlled Trials

Randomized Controlled Trial (RCT) is a type of scientific experiment used to test the efficacy and efficiency of a service in healthcare, such as a new technology, methodology, treatment or drug therapy in a well-designed target population following a rigorous methodology. In an RCT, the population is divided into two groups and every individual willing to be part of the test is allocated to one group or another by randomization: the experimental group and the control group. The new treatment is delivered to one group (experimental) and the other treatment (usual care) is delivered to the other group (control). A RCT starts from the formulation of a clinical question

Fig. 1.3 shows the schematic diagram of an RCT:

1. a population of eligible patients is identified;
2. a group of patients, eligible according to the predefined inclusion and exclusion criteria, is recruited from this population, after signing a proper informed consent, approved by an Ethical Committee;
3. at least two group are created;
4. participants are allocated to the groups by randomization;
5. outcome measures from both groups are collected and compared.

1.3.1 Key elements of RCT

The need of randomization

Randomization refers to the participant's allocation process to the treatment(s) or control group. Random allocation will equalize individual differences between groups allowing, as far as possible, the treatment effect to be established uncontaminated by other potentially competing factors. In other words, random allocation aims to minimize the effect of possible confounds, leading to a fair comparison between the treatment(s) under investigation and the other procedure chosen as control.

The need of a control group

In RCT, the control group is required to assure that the effects are only due to the novel treatment under investigation and not to spontaneous changes, it has to be compared with the best treatment currently available. If there is no accepted treatment available, then the control group may receive no treatment at all, or they may receive a sham treatment (i.e., placebo).

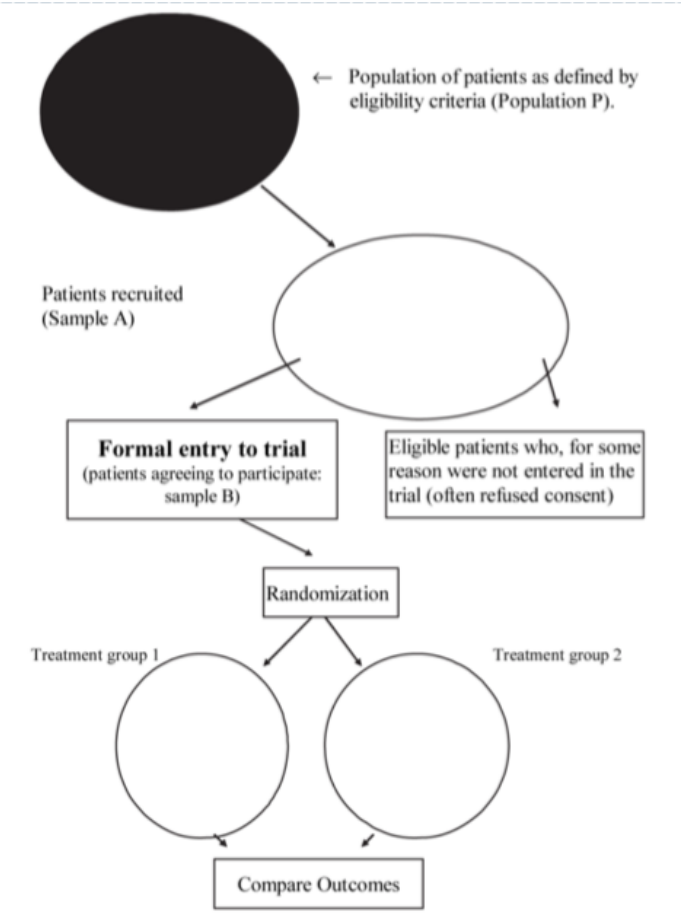

Figure 1.3: *Schematic diagram of an RCT.*

The need of a statistical approach

A treatment results in different outcomes on a patient-by-patient base, even in a homogeneous population. To assess the efficacy of a treatment on a population base, RCTs require a robust statistical approach. Indeed, as first step researchers have to well-define the target population and outcome measures. In this way, they can determine the required sample size to obtain the statistical power. Specific algorithms have been proposed to define the sample size according to the set primary outcome measure, and its variability, or minimal clinical difference, and the aimed power of evidence. Then, the RCT analyzes the mean behavior of a target population and draw solid conclusions.

1.4 Ethical issues

The World Medical Association establishes the Declaration of Helsinki in 1964 to provide ethical universal rules to conduct clinical medical research. Since 1964, it has been reviewed several times lastly in 2013. No valuable medical journals publish studies whose design it not based on its principle. The Declaration of Helsinki is composed by the following main points:

- The experiments have to be performed in compliance with the respect of the patient
- A treatment known to be inferior should not be given to any patients
- The privacy of patients has to be guaranteed
- Participation is voluntary and the patient can withdraw with the study in any moment
- An informed written consent has to be signed by each participant before enrolment
- Research can be conducted only if the importance of the objective overtakes the risks
- A clear research protocol should be established

To guarantee the transparency and the independence of the ethical committee from the interests of a single category (i.e., the researchers or the sponsor) it is composed by individuals with difference competences, not related to the research. It include clinicians, biostatisticans, patients, expert in medical devices, in bioethics, and in insurance issues. The ethical approval is mandatory before the beginning of any clinical study. At the end of the study, the researchers have to submit to the ethical committee a

report summarizing the main results of the study. Recent guidelines also require that the RCT is registered in publicly available registers, such as https://clinicaltrials.gov/

1.5 Systematic errors and bias

A bias is a systematic error or a deviation from the truth in results or inferences. Biases can lead to both underestimation or overestimation of the true intervention effect [2]. Therefore, the evaluation of the risk of bias in clinical trials is required to lower the probability of formulating incorrect decisions about treatment effects.

1. SELECTION BIAS: It occurs when the person, who enrolls the patients in the study, knows in advance the allocation to the treatment group. Indeed, it this case he/she can be influenced in the decision to enroll the patient.

2. ALLOCATION BIAS: The randomization procedures should be designed to balance groups at baseline with particular attention to prognostic factors that can influence the outcome.

3. ASSESSMENT BIAS: it can occur when the assessors are not blinded to treatment allocation, and thus can be influenced in his/her evaluation, mainly when outcome measures characterized by low sensitivity, high subjectivity (such as patient reported outcomes) and low inter and intra-rater variability. Assessment bias can occur also when patients are not blinded to treatment allocation, since he/she can behave differently during the assessment.

4. PUBLICATION BIAS: The ultimate goal of any medical research is to influence clinical practice. Thus, the findings of a RCT have to be published in scientific international journals. To be published papers undergo a peer-review process, and often papers with positive findings are considered more likely to be published than papers that do not show any statistically significant differences. This can lead to a publication bias as medical research not equally reports study with positive and negative results. To reduce publication bias, it is essential to register all studies undertaken in an international recognized repository, such as https://clinicaltrials.gov/, in which the Principal Investigator should declare and describe the whole methodology.

5. STOPPING RULES: A-priori sample size is not trivial. Recruitment too few patients may prevent the achievement of a definitive result on the superiority of a treatment over the other. On the other hand, recruiting more patients than necessary may become unethical as the surplus patients could be exposed directly to the superior treatment.

1.6 CONSORT

Well-designed and properly executed RCTs provide the most reliable evidence on the efficacy of a healthcare intervention but trials with inadequate methods may overestimate the treatment effect. Biased results from poorly designed and reported trials can mislead decision making in healthcare at all levels, from treatment decision for a patient to formulation of national public health policies. A critical judgement of the quality of clinical trials is possible only if the design, conduct and analysis of RCTs are accurately described in the report. To improve the quality of reporting of RCTs, the CONSORT statement has been developed. CONSORT stands for Consolidated Standards of Reporting Trials. It includes a checklist of 25 items that should be included in reports of RCTs. The most important items are listed in Sec. 1.6.

1.7 Systematic Reviews

When dealing with complex technologies, the demonstration of the effectiveness of their use is rather difficult to be demonstrated following the canonical research studies design (i.e., RCT design). This is due to several reasons, such as difficulty to demonstrate the validity independently from the users' placebo effect (e.g., it is impossible to perform a blind session), the high cost of the technology and therefore the impossibility to recruit many volunteers contemporary, and the Ethical Committee procedures for non CE-marked devices. In this view, a meta-analysis might be the needed approach. Meta-analysis is defined as the statistical analysis of a collection of analytic results for the purpose of integrating the findings. Such analyses are becoming increasingly popular in medical research, where information on the efficacy of a treatment is available from a number of clinical studies with similar treatment protocols. If considered separately, each study may be either too small or too limited in scope to come to unequivocal or generalizable conclusions about the effect of a treatment. Combining the findings across such multiple, yet small, studies represents an attractive alternative to strengthen the evidence about the treatment efficacy.

The Cochrane Collaboration is an international organization whose primary aim is to help people make well-informed decisions about health care by preparing, maintaining, and promoting the accessibility of systematic reviews.

1.7.1 Key characteristics of systematic reviews

According to the Cochrane Handbook for Systematic Reviews of Interventions, the main features of systematic reviews are the following:

- A clear set of objectives with pre-defined eligibility criteria for studies

Trial design (n. 3)	Description of trial design, information about the procedure and allocation to groups
Participants (n. 4)	Inclusion and exclusion criteria for participants, information on the settings and locations where the data were collected
Interventions (n. 5)	Precise information about the delivery of the treatment to each group
Outcomes (n. 6)	Definition of pre-specified primary and secondary outcomes, including information about the time of their assessments
Sample size (n. 7)	Authors should specify the primary outcome on which the calculation of the sample size was based and all the quantities used in the calculation, and the resulting target sample size per group. The choice of the sample size is based on the statistical significance and the assumed distribution of the studied variables
Randomization (n. 8-9)	Specification of sequence generation (i.e., method used to generate the random allocation sequence), type of randomization, specification of allocation concealment (i.e., mechanism used to implement the random allocation sequence)
Blinding (n. 11)	Specification who and how was blended about the allocations to single groups after the assignment to interventions (for example, participants, care providers, assessors)
Statistical methods (n. 12)	Statistical methods used to compare the outcomes (both primary and secondary) from the different groups, methods for additional analyses, such as subgroup analyses and adjusted analyses. Outcome measures are usually collected at baseline, post-treatment, and after the follow-up. Significant tests of baseline differences (e.g. student's t-test for independent samples) are common in RCT. For continuous variables, under the assumption of a normal distribution, we use parametric tests, while for categorical variables or without the assumption of a normal distribution we use non parametric tests
Results (n. 14-16)	Results section should report: i) recruitment (i.e., dates defining the periods of recruitment and follow-up, why the trial ended or was stopped), ii) baseline Data (i.e., a table showing baseline demographic and clinical characteristics for each group), iii) numbers analyzed (i.e., for each group, number of participants included in each analysis and whether the analysis was by original assigned groups
Discussion (n. 20-22)	Discussion section should report: i) trial limitations, ii) generalizability of the findings, and iii)interpretations of the results, balancing benefits and harms, and considering other relevant evidence

Table 1.1: *CONSORT guidelines.*

- An explicit and reproducible methodology
- A systematic search to identify all studies that meet the eligibility criteria
- An assessment of validity of findings of the included studies
- A systematic synthesis of the characteristics and findings of the included studies

1.7.2 How to perform a systematic review

Defining the review question

The criteria for considering types of people included in studies in a review should be sufficiently broad to encompass the likely diversity of studies, but sufficiently narrow to ensure that a meaningful answer can be obtained when studies are considered in aggregate. The characteristics of studies included in the review are usually defined with the PICOS format:

- Participants: what are the characteristics of the patient or population? What is the condition or disease you are interested in?
- Intervention: what do you want to do with these participants (e.g., treat, diagnose, observe)?
- Comparison: what is the alternative to the intervention (e.g., placebo, different drug, surgery)?
- what are the relevant outcomes?
- Study: which is the study design you are interested in?

According to the PICOS format, the researchers define the inclusion and exclusion criteria for studies.

Searching for studies

Then, researchers perform a comprehensive electronic search on bibliographic database. The most important sources are CENTRAL, MEDLINE, EMBASE, Scopus.

Selecting studies

Assessment of eligibility of studies should be done by at least two people, independently. The typical process is performed as follows:

1. Merge search results from different databases and remove duplicate records

2. Examine titles and abstracts to remove obviously irrelevant reports
3. Retrieve full text of potentially relevant reports
4. Link together multiple reports of the same study
5. Examine full-text reports for compliance of studies with eligibility criteria
6. Correspond with original authors, where appropriate, to clarify study eligibility
7. Make final decisions on study inclusion and proceed to data collection

Collecting data

Extraction of data from study reports, should be done by at least two people, independently. The following data are usually collected:

- Methods (study design, study duration, randomization, blinding)
- Participants (number, setting, criteria, age, sex, etc)
- Interventions
- Outcomes (scales, time points)
- Results: number of participants allocated to each intervention group, summary data for each intervention (e.g., 2x2 table for dichotomous data; mean and SDs for continuous data).

Data are presented in the table of "Characteristics of included studies".

Assessment of risk of bias

The extent to which a meta-analysis or a systematic review can draw conclusions about the effects of an intervention depends on whether data and results from the included studies are valid. The validity of a study may be considered to have two dimensions. The first dimension is whether the study is asking an appropriate research question. This is often described as "external validity" and its assessment depends on the purpose for which the study has to be used. External validity is closely connected with the generalizability or applicability of study findings. The second dimension of study validity relates to whether it answers its research question correctly, that is, in a manner free from bias. This is often described as "internal validity". Bias can lead to underestimation or overestimation of the true intervention effect. The following types of bias are usually analyzed:

- SELECTION BIAS: Systematic differences between baseline characteristics of the groups that are compared
- PERFORMANCE BIAS: Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest
- DETECTION BIAS: Systematic differences between groups in how outcomes are determined
- ATTRITION BIAS: Systematic differences between groups in withdrawals from a study
- REPORTING BIAS: Systematic differences between reported and unreported findings

1.7.3 Meta-analysis

Meta-analysis uses statistics to derive a pooled estimate of the effect of the treatment closest to the unknown common truth. Thus, a systematic review refers to the entire process of selecting, evaluating, and synthesizing all available evidence, while the term meta-analysis refers to the statistical approach to combining the data derived from a systematic-review. Conclusions produced by meta-analysis are statistically stronger than the analysis of any single study, due to increased numbers of subjects, greater diversity among subjects, or accumulated effects and results. Meta-analyses have become common in the social and biomedical sciences. A final overall quality of the evidence and strength of recommendation is then assessed by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) methodology [**?**]. The GRADE defines the quality of a body of evidence as the extent to which the investigator can be confident that an estimate of effect or association is close to the quantity of specific interest. The GRADE approach specifies four levels of quality: high, moderate, low and very low, as defined in Tab. 1.2.

Grade	**Significance**
High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

Table 1.2: *GRADE certainty ratings.*

Chapter 2

Rehabilitation Robotics

2.1 Context

In the last decades, we assisted to a huge progress in the healthcare and technology field, that lead to improvements in the acute care. At the same time, the life expectancy has increased, and consequently the society is aging. It implies that a number of people with chronic disability and neurological disorders is increasing, resulting in an higher request of hospitalization and rehabilitation treatments. Chronic diseases imply high cost for the society.

Rehabilitation, and more in general technology, plays an important role in recovering and keeping a state of health of patients. However, the most important and basic concept is always the education: a better nutrition and a greater physical activity improve the quality of life. The health condition is made by how the interaction between the person and the environment is achieved in terms of Body Functions and Structures, Activity, and Participation according to the International Classification of Functioning, Disability and Health (ICF) [3]. The ICF is a classification of health and health-related domains. As the functioning and disability of an individual occurs in a context, ICF also includes a list of environmental factors (Fig. 2.1). ICF is the World Health Organization (WHO) framework for measuring health and disability at both individual and population levels. ICF was officially endorsed by all 191 WHO Member States in the Fifty-fourth World Health Assembly on 22 May 2001 as the international standard to describe and measure health and disability.

2.2 Service Robotics

Service Robotics aims to create a multitude of robotic device to assist humans in daily activity and enhance the ability of caregivers and family member to take care of their

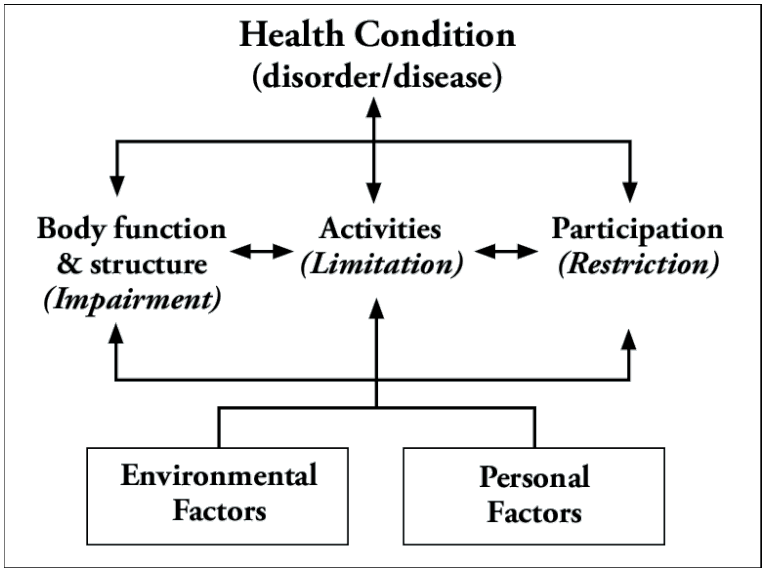

Figure 2.1: *International Classification of Functioning, Disability and Health [4].*

clients and relatives. It can be divided in:

- Orthotics;
- Rehabilitation Robotics.

Orthoses aim at improving functions in people with a weak limb due to a neurological disorder who cannot properly control it when interacting with the environment (i.e., assistive technologies). They are passive or powered external devices for the neck, upper limb, trunk, and lower limb that are designed to guide motion, bear weight, align body structures, protect joints, or correct deformities. Unlike prostheses that replace a body part, orthoses are designed to work in cooperation with the intact body, and either control or assist movement [5]. There are several upper and lower limb orthoses being developed to actuate specific joints. They offer the promise of combining and blending assistive and rehabilitation technology into a single field. For example, it would allow community dwelling people recovering from a stroke to perform functional tasks at home or anywhere with the concomitant rehabilitative potential.

Rehabilitation robotics, instead, develops tools to assist the clinicians in promoting rehabilitation of an individual so that he/she can interact with the environment unassisted. Rehabilitation devices use are confined in a specific period of time.

The main difference between the two is related to the costs. Orthotic devices are meant to be used by a single end-user (i.e., the patient), so they must have a lower costs. Rehabilitation devices are usually used in the hospital/rehabilitation clinics, and are used for more than one patient, so their cost is higher.

2.3 Stroke

Stroke is the second cause of death and the third leading cause of severe disabilities worldwide [6]. There are two main causes of stroke, associated to a fast-cerebral functionality loss: a blocked artery (i.e., ischemic stroke), or leaking/bursting of a blood vessel (i.e., hemorrhagic stroke). Some people may have only a temporary disruption of blood flow to the brain, known as a transient ischemic attack (TIA), that does not cause lasting symptoms. Immediately after the stroke, as reported by Cramer et al. [7], more than 80% of the patients is affected by hemiparesis, connected to loss of muscular tone. Stroke usually affects one side of the brain, and functional deficits are contralateral with respect to the cerebral lesion. Despite the extensive resources devoted to stroke rehabilitation and aftercare, stroke still remains a devasting disease. Winstein et al. [8] underline as clinical trials in this field have been few and have been conducted only in the past decade. According to Bejot et al. [6], at the beginning of the 21st century, approximately 1.1 million inhabitants of Europe suffered a stroke each year, and ischemic stroke accounted for approximately 80% of cases. Although global stroke incidence is declining, rates observed in young adults are on the rise, thus suggesting a need for strategies to improve prevention. However, because of the previous mentioned ageing of population, the absolute number of strokes is expected to dramatically increase in coming years: by 2025, 1.5 million European people will suffer a stroke each year.

As most patients survive the initial injury, the biggest effect on patients and families is usually through long-term impairment, limitation of activities of daily living (ADLs), and reduced social participation. In this context, rehabilitation robotics can offer to fill this gap in the clinical ambit, parallel to the continuous research in this same field. Being the most likely cause of long term disability, stroke is, under a market analysis point of view, the major target population of development of new orthoses and rehabilitation robots. As a fallout the same technologies can be used also in other pathologies having similar symptoms, similar disability, but lower incidence and prevalence, such as neurodegenerative pathologies, such as Multiple Sclerosis, and orthopedics patients. The use in different pathologies anyway, implies proper actions by the producer in term of certification of the device and evaluation of its clinical effectiveness.

2.4 Neuroplasticity

In recent years, convincing evidence has been produced in neuroscience that has led to the knowledge that the brain can change or reorganize itself to recover after disorders or injuries [9]. This adaptive potential of the nervous system is called neuroplasticity.

Neuroplasticity defines all the modifications in the organization of neural compo-

nents occurring in the central nervous system during the entire life span of an individual [10]. Such changes are thought to be highly involved in mechanisms of aging, adaptation to environment and learning. Moreover, neuronal plastic phenomena are likely to be at the basis of adaptive modifications in response to anatomical or functional deficit or brain damage [11]. Ischemic damage causes a dramatic alteration of the entire complex neural network within the affected area. It has been amply demonstrated that the cerebral cortex exhibits spontaneous phenomena of brain plasticity in response to damage [11, 12]. The destruction of brain areas, indeed, stimulates a reorganization of the connections, and this rewiring is highly sensitive to the experience following the damage. Such plastic phenomena involve particularly the perilesional tissue in the injured hemisphere, but also the contralateral hemisphere, subcortical and spinal regions.

In the period following an injury to the central nervous system, two phases can be generally distinguished, each characterized by different functional changes and therefore these differences will have to be considered during the therapy for rehabilitation purposes:

1. Short-term plasticity phase in which biochemical, biophysical, vascular and neurovegetative plastic changes are observed.

2. Long-term plasticity phase in which morphological and functional neuroplastic changes are observed above all.

It is also interesting to mention how research, in the in the last decade, described a different type of neural plasticity due to the injury and the excessive training, named "maladaptive plasticity" [13]. Clinically, this phenomenon is relevant when, for example, the functions of the upper limbs movements are replaced with compensatory or substitutive movements and the delayed onset involuntary abnormal movements. Several studies have reported that maladaptive plasticity weakens motor function, limiting motor recovery after stroke.

Physiotherapy strategies used during recovery process affect the spontaneous neuroplasticity [14]. The goal of rehabilitation is, thus, to maximally exploit neuroplasticity in order to achieve an optimal outcome for the individual patient. However, neuroplasticity is limited, with most patients reaching a plateau after recovering approximately 70–80% of the initial impairment. The recovery of function in persons with CNS lesion is much like a relearning process exploiting preserved sensorimotor circuits. The relearning can be optimized by providing appropriate proprioceptive input to the spinal cord with the goal of maximally engaging preserved neural circuits [15].

2.5 Key ingredients of motor re-learning

The key ingredients for motor re-learning that have to be considered, in order to promote neuroplasticity, are:

- **Amount of practice**: the more practice and exercise, the greater success.
- **Early intervention**: it has been demonstrated that there is a window of enhanced neuroplasticity early after stroke, during which the brain's dynamic response to injury is heightened. and rehabilitation might be particularly effective [16].
- **Functional and goal-oriented training**: the ability to perform a specific functional task contributes in the process of neuroplasticity. The link between function and intention promotes the maximal recruitment of synergistic brain areas involved in real life functions. The complexity of interplay of these areas should be called also during rehabilitation training
- **Biofeedback and Augmented information**: biofeedback is a process that uses instruments to make information about the body available to the mind. During the rehabilitation, it is useful to have multiple sources of information provided to the patient him(her)self about what the ongoing performed tasks. The sense of proprioception can be disturbed in many neurological disorders and stroke patients. Biofeedback and augmented proprioception in these patients can improve the process of motor re-learning. Providing a continuous feedback about the movement is a key element for training, allowing the process of error compensation to occur (without feedback error is not available). For instance, the stroke will lead to a lateral impairment: if we ask a patient to pedal, the healthy leg will do an extra job to compensate the other leg. This is a functional rehabilitation, but it will not lead to re-learning because the patient will use mostly the healthy leg, as a compensatory solution to achieve a good function. So it would be better to provide a bike that gives the information of how much he has to push with each leg: this is the feedback that the patient needs to re learn the movement and check the real work done by the paretic side.
- **Repetitive training**: training needs repetition, indeed learning comes from errors, and repetitions. Increased repetitions bring to greater skills.
- **Rewarding, interactive and engaging task**: The motivation of the patient is a key element for the success of re-learning. Reward and encouraging is essential for the subject, which is asked to perform simple tasks as many time as possible,

often experiencing fails "if I can't do it once, why shall I repeat it a hundred time?".

- **Volitional contribution**: if the patient has some residual capabilities, it is important that the patient is conscious, and he/she tries to do the movement instead of being passive during it. Indeed, in this way we can enhance neural plasticity, by activating motor planning pathways.

- **Individualized training**: every patient is different, so we need to propose a custom rehabilitation tailored to the needs and the improvements of each patient.

- **Continuity of therapy**: it mainly deals with a loop of monitoring, exercising, and being adherence to therapy. Further, hospitalization needs to be limited in time, for psychological aspects as well as for costs, but proper therapy needs to continue even for outpatients.

Summing up increased practice leads to greater skills, as long as practice is challenging, progressive, and skill based and the subject is fully engaged. These are the goals that rehabilitation therapy should achieve.

2.6 Limitations of conventional therapy

Conventional therapy fundamental is the relation between the therapist and the patient and the expertise of the therapist. Engagement, treatment customization, feedback to the patients are all elements which are directly driven by the therapist. This implies that the therapist-patient is a one-to-one work, being the cost of manpower the most relevant in the cost-effectiveness analysis. However, the severity of impairment prevents certain patients from practicing, especially when more physicians are needed for the support of the severe impaired patients. The shortage of physicians represent the major bottleneck of the system, limiting the number of training hours to a few even in hospitalized patients. Unfortunately, the practice is often confined to boring repetitive passive mobility tasks, where the sustain of patient's motivation become a great challenge. Furthermore, the lengthy rehabilitation process contributes to a poor motivation of patients. As the patients achieve different stages of recovery their needs are changing and a continuous evaluation should be carried out, but it is usually not available and so it is the experience of the therapist which drives the adaptation of exercises to the single patient's improvement profile. Furthermore, the limited number of repetitions of exercises and specific tasks, which ends out to be boring both for the therapist and the patient, is contributing to a very slow and often inappropriate therapy.

2.7 Robotics as a solution

2.7.1 From Neuroplasticity to Robotics

The focus is to translate neuroplasticity principles into technologies design that fits into specific rehabilitation programs, allowing the recovery of the patient's abilities over time. Patients need continuity of care, and this is a problem that has to be solved. To tackle the challenges that have been highlighted for improving motor re-learning, the design and clinical translation of safe, simple, immersive and functional devices is needed for assuring the maximal recovery during the hospitalization, as long as after the discharge, and eventually at home. Evidence-based assessment of rehabilitation therapies' alternatives (including robotics assisted therapy, training adopting neuroprostheses and hybrid assistive devices, as well as conventional treatments) is a milestone in the view of the customization of treatments on single patient.

2.7.2 What is rehabilitation robotics

Rehabilitation robotics is a field of research dedicated to understanding and augmenting rehabilitation through the application of robotic devices. It includes development of robotic therapies, and the use of robots as therapy aids instead of solely as assistive devices.

Up to now, a wide range of strategies and devices have been developed for promoting motor recovery after stroke by taking advantage from the brain ability to reorganize its functional connectivity after the injury [17]. Traditional approaches towards rehabilitation can be qualified as "bottom-up" approaches as they operate at the peripheral effectors and expect for central nervous modifications [18]. Currently, robotic technologies and mechatronic devices represent the modern version of bottom-up treatments providing a high dosage of task-oriented training to patients affected by different degree of functional impairment [19]. Robotic training can increase the intensity of therapy, and bring down the requirement of therapist assistance during rehabilitation therapy, with an eventual decrease of costs for the health care system [20]. This applies specifically in case of gait impairment, where more than one therapist are usually required for safety issues in usual care at the first gait training sessions, or the gait training is put off for safety reason, limiting the exploitation of the early intervention..

2.7.3 General features of robotic devices

Robotic systems have many properties, as high repeatability, possibility to perform a great amount of exercises in a single session and high intensity of task-oriented training [21]. Many of these devices can be also adapted for the needs of the patients, allowing

for a customization of the therapy. For example, exoskeleton-based systems can be tailored based on the length of the patient arm's segments whereas end-effector-based devices can provide different types of motor exercises in agreement with the spared motor patient's ability [22]. Furthermore, recent studies have also attempted to improve motivation in stroke rehabilitation using these robotic devices coupled with elements of virtual reality and exergames (e.g., audiovisual elements, score displays and cognitive challenges). Indeed, motivation promotes exercising for longer periods, increasing the total amount of training. Variegate game environments assure a high level repeatably of tasks reducing the boredom of the treatment. These devices incorporate several sensory components (e.g., encoders, accelerometers, load cells, etc.) allowing for a complete feedback and monitoring of the therapy progress over the time, even adjusting the degree of robot assistance based on the progress of the patient. Thus, it is possible to obtain a continuous evaluation of patient's motor performance that is extremely accurate and objective [23]. Several kinematic and kinetic measures can be recorded offering a complementary evaluation of the motor performance with respect to traditional methods, i.e., clinical scales [24]. Several parameters are used to quantify performance, such as the smoothness of the movement, the mean speed, the movement accuracy, the mean arrest period and also the details of the constituent sub-movements [25, 26]. Upper limb weakness (i.e., lack of strength) is another common consequence of stroke and its time evolution is an important clinical parameter. Robotic systems can continuously monitor the force signal exerted by the patient by means of force sensors (i.e., pressure sensors or load cells) and extract important parameters as average force amplitude, direction and number of force peaks performed during the motor task [27, 28].

2.7.4 Classification of robotic devices

Beside the extremity being trained, the rehabilitative robotics can be classified into grounded exoskeletons, end-effector devices and wearable exoskeletons (Fig. 2.2) [29].

End-effector devices are devices that apply mechanical forces to the distal segments of the limbs. They are easy to setup and control, however there is no supervision of proximal joins and also the possibility of abnormal movement patterns. Exoskeleton devices are devices in which the robot axes are aligned with the anatomical axes of the subject. The advantage is that there is direct control of the individual joints and minimization of abnormal posture. However, these systems are much more complex and expensive. Maciejasz et al. [22] explain as the mechanical and control algorithm complexity of exoskeleton-based systems is usually higher than the end-effector-based devices, because of the need to manage the high number of movements and to adjust lengths of particular device's segments to the lengths of the patient arm segments.

Tab 2.1 reports the main advantages and disadvantages of using these devices.

	EXOSKELETON	**END-EFFECTOR-BASED**
PROS	- Joint axes fully determined - Physiological movements - Force and Position data of each point	- Simpler structure/control - Easy to adjust to patient
CONS	- Robot axes have to align with anatomical axes - Longer set-up times - Challenging anatomical constraints	- Limb posture not fully determined - Limited force/position data - Risk to joint injury

Table 2.1: *Exoskeletons and end-effector robots in rehabilitation: analysis of pros and cons*

The type of robot being used in the therapy strictly depends on the current state and possibilities of the patients. Severely affected patients can benefit from passive/highly-assisted movements and gravity support by exoskeletons that provide control over all relevant joints. While for the less affected patients might be more beneficial to use end-effector devices, as there is a high possibility for abnormal movement patterns, that might hurt the patient [29]. Note that patient safety is the first mandatory requirement when choosing the type of device and control strategy.

2.7.5 Robotic strategies to provoke plasticyty

The goal of robotic therapy control algorithms is to control robotic devices designed for rehabilitation exercise, so that the selected exercises to be performed by the participant provoke motor plasticity, and therefore improve motor recovery. Basing on the review by Marchal-Crespo [30], one way to group current control algorithms is according to the strategy that they take to provoke plasticity:

- **Assistive controllers**: The robot is helping the subject in achieving the task. It is the primary control paradigm that has been explored so far in robotic therapy development. In this context, the robots needs to be powered. Multiple solutions can be designed in order to tune the collaboration between the robot action and the user's residual capabilities. In completely powered solutions, the robot drags the arm of the user to achieve a task , which corresponds to passive mobilization done by therapists. In partial weight support, the robot supports partially the weight of the arm in order to facilitate the autonomous task accomplishment by the user.

- **Challenge-based controllers**: the robot is making the task more difficult (resisting the task or amplifying the error). Thanks to this approach, the patient is

UPPER LIMB ROBOTICS	
Powered devices	Provide an active motion assistance (at least one actuator).
Non-powered devices	Non-powered support of the limb during movement attempts. Support is offered with elastic bands, springs or counterweights.
Interaction devices	Combine actuators and control strategies allowing for the correction of "wrong" motor exercise, but also for the modification of the control parameters based on ongoing performance.

Table 2.2: *Upper limb robotics classification.*

always challenged during the session. If he/she is performing better (i.e., lower error), then he/she is required to perform with more effort.

- **Haptic simulation with Virtual Reality**: the robot is integrated into a virtual environment and is offering an haptic feedback, in order to mimic activity of daily life.

- **Non-contact coaching**: the robot is not worn by the user. It is in front of the subject, supporting him/her and checking if the person is doing the task (e.g., NAO ROBOT). This kind of control is used, for example, in autism therapy.

2.8 Robotics for upper limbs

According to [30], they can be classified as reported in Sec. 2.8 based on the different type of motion assistance they can provide. Note that separation between the classification is not hard, a robot can have both active and passive components (springs elastic bands and motors). Passive components are usually adopted to limit power supply for weight bearing.

2.8.1 Control strategies for upper limb robots

Concerning the upper extremity, impaired arm and hand function contributes considerably to limitations in the ability to perform activities of daily living (ADL). The utmost goal of post stroke rehabilitation is to allow the patient to perform ADL independently. Most of the robotic devices applied in clinical practice offer the possibility of choosing among four modalities for training: active, active-assisted, passive and resistive. [31]. These terms refer to subject's status during interaction. In active mode, performance arises from subject's contribution and the robot is transparent and used for monitoring and for integration with exergames or virtual reality. In passive mode

the movement is performed by the robot regardless of subject's response. In active-assisted mode, the user performs active movement at the beginning and the robot acts only in particular conditions (i.e., if the target has not been reached in the requested time), systematically leading to success. Finally, resistive mode consists of resisting the movement received from the subject, so the robot makes the movement quite more difficult. On this background, the "assistance-as-needed" control was conceived to encourage patients' active motion. In this approach, the robotic device is able to either assist or correct the movements of the subject, with the aim to manage simultaneous activation of efferent motor outputs and afferent sensory inputs during training [32]. Current assist-as-needed strategies aim to provide the suitable definition of the desired upper limb trajectory in space and time the robot must generate to assist the subject during the task.

The official reference for control strategies for rehabilitation robotics is the Marchal Crespo paper [30] and the Proietti et al 2016 [33] article which will be discussed in the Journal Club of next Friday and Monday.

2.8.2 Current evidence from clinical trials

Robotics devices for rehabilitation demonstrated high advantages with respect to conventional therapy. However, the clinical evidence supporting their use is still not clear.

For what concerns end-effectors, there are several studies comparing these devices with conventional therapy. A comparison between conventional therapy alone and robotic training combined with conventional therapy have been done in a sample of 56 subacute stroke patients [19], and the latter approach showed a greater improvement. This datum stands for a positive impact of end-effector devices on upper-limb recovery in patients in the subacute phase of stroke, thus recommending their use. Differently, another study conducted on a large sample of chronic stroke patients [34] showed that robot-assisted upper limb training with end-effector device and intensive conventional therapy determined the same degree of clinical improvement after 12 weeks of rehabilitation, although after further 24 weeks of treatment the robotic approach resulted in greater improvement. Another study involving chronic patients [35] compared high-intensity robot-assisted training with control treatment group and low-intensity robot-assisted training with control treatment group and found significantly greater improvement after robotic training only when performed in the high-intensity modality. These insights indicate that the intensity is the most relevant parameter in the rehabilitation of upper limb with robotic devices in chronic stroke patients, when end-effector are used. An effect of robot-assisted therapy on ADL function is observed only in patients with subacute stroke [36].

RATULS trial [37], a Randomized Controlled Trial involving 770 patients, high-

lighted that MIT-manus based robotic training led to improvement in upper limb impairment (as detected by the Fugl-Meyer Assessment motor subscale) compared with usual care (i.e., Body Structure and Function domain), but not improvements in upper limb function or ADL (i.e., Activity domain). Enhanced Upper Limb Therapy (EULT), in which training specifically focused on daily activities and functional tasks, led to improvements compared with usual care at the end of the intervention period (at 3 months) for both Body Structure and Activity domains. Recent meta-analyses [38] revealed a small, heterogenous, but significant effect of robot-assisted rehabilitative interventions on motor functions and upper extremity recovery with unclear clinical impact due to the relative small effective size.

As regards Exoskeleton-type robot devices for upper limb recovery, almost all trials performed up to now comprised patients in the chronic stage of stroke. Among them, one study reported a significantly better effect on spasticity in the robot-assisted therapy group than in the conventional therapy group [39]. In contrast, ADL function improved more markedly in the conventional therapy group that received the same amount of treatment. Other reports demonstrate no significant difference between robot-assisted therapy with exoskeleton devices and conventional therapies [40, 41]. In addition, there are no randomized controlled trials that investigate robot-assisted therapy with exoskeleton devices in patients with subacute stroke. Therefore, at this time there is an insufficient evidence to draw a definite assertion as to what is the real effectiveness of exoskeleton systems for the rehabilitation of upper limb after stroke.

A very recent review paper [42] proposed a long-standing view that in clinical settings robotic therapy should focus on impairment training, combined with therapist transition-to-task training, to translate the impairment gains into function.

2.8.3 Example of devices

MIT-MANUS

One of the best-studied end-effector robots for the upper limb is the MIT-MANUS robotic system, commercially available as the InMotion series of devices InMotion/Bionik. The system is composed of proximal and distal components, which can be used individually or in concert to train the upper limb. These configurations include a module for elbow and shoulder movement in the horizontal plane, shoulder and hand grasp in the vertical plane, and wrist movement in all planes. Usually, the device employ an assist-as-needed paradigm, continually sensing motion of the limb and initiating or completing movements to complete a programmed simulated task. The therapeutic exercise game is the most studied mode, that achieves 1000 movements in a single session.

Armeo Power

Armeo Power is probably the most advanced robotic exoskeletal workstation device for the upper limb currently on the market. The device is composed of a workstation with an exoskeleton enveloping the user's arm, that can be adjusted for shoulder height and limb length. Also it provides arm weight support, that offsets the weight of the device and a designated proportion of a patient's limb weight. Additionally, the Armeo Power uses custom software, that enables the device to be used in various ways. It offers a mobilization mode, 2D gaming, 3D gaming, and functional training in the form of simulated activities of daily living. The Armeo Power excels in the area of patient engagement, uses robust graphics and simple, yet engaging, games to promote repetitive movement. The software enables the clinician to select the appropriate challenge by controlling the complexity of the visual field, defining the range of motion required, and designating the pace of gameplay. Similar to the MIT-MANUS, the Armeo Power employs an assist-as-needed model, allowing the clinician to provide the optimal challenge at all levels of recovery. Additionally, this technology enables stabilization of specific joints during gameplay, enabling the clinician to select a modular or composite approach to treatment, as desired.

Bi-Manu-Track robotic arm trainer

An alternative approach to upper limb robotic treatment is a bilateral treatment strategy. An example of this approach is seen in the Bi-Manu-Track, that consists of dual forearm troughs mounted on a tabletop workstation. It provides mirrored movements to the upper limbs including forearm pronation/supination, wrist flexion/extension, and metacarpophalangeal extension. The device can provide passive bilateral movement, mirror movements produced by the unaffected/affected arm, or provide resistance to movement.

DIEGO

The design concept in workstation robotics, utilizes cables to support and mobilize the upper limbs less used concept. One of them is the commercially available DIEGO (Tyromotion). It utilizes an overhead boom with four suspended cables, which connect to slings at the wrist and elbow. The device can be applied unilaterally or bilaterally and em- ploys "intelligent gravity compensation" to unweight the limb and facilitate motion in three dimensions, much like a mobile arm support. Support can be withdrawn over time as patients progress from passive to active therapy modes. The DIEGO expands upon the idea of gaming as a means of patient engagement by integrating specially designed cognitive games, in an effort to pair upper limb training with cognitive reme-

diation. Most notably, the device can also be used to enable supported performance of actual tabletop functional tasks. The design of the DIEGO enables it to offer the versatility and rapid setup of an end-effector device, with the added benefit of direct application to functional activities.

Hand of Hope

The Hand of Hope (Rehab-Robotics, Hong Kong) is a semi-wearable hand exoskeletal device. The Hand of Hope uses a biofeedback approach, detecting a user's intent through surface electromyography and responding with exoskeleton-driven grasp or release. In a study of ten subjects with chronic stroke, a training program using the Hand of Hope resulted in statistically significant improvements in functional performance as well as enhanced muscle coordination, as measured by EMG.

Wearable devices

Myomo

The MyoPro Motion-G is a lightweight, wearable orthosis for the upper limb. The device can be noticed that it fits like a sleeve on a person's arm. It has sensors that are placed on the skin's surface and detect even a very faint muscle signal [ref]. It detects electomyographic signals from the limb to sense a user's intention and responds by providing assisted elbow flexion/extension or grasp/release.

My hand

The MyHand device, currently in development, targets individuals with gross grasp, but insufficient functional release of the hand. The device seeks to capitalize on the residual capacities of the upper limb post-stroke in order to provide both a training mechanism and neuroprosthetic utility for home-use. The MyHand device is designed to be low-cost and to accommodate patients with a range of residual capacities, including those with in- sufficient EMG to operate other devices. A number of control mechanisms, including contralateral and ipsilateral manifestations, are in development.

2.9 Robotics for lower limbs

Robotic systems for gait recovery can be essentially divided in two main categories: end-effectors or electromechanical exoskeletons. Examples of end-effector devices are the "G-EO-System" (Hesse et al., 2010), the "Lokohelp" (Freivogel et al., 2009) and the "Gait Trainer GT 1" (Hesse et al., 2010). End-effector systems are characterized by the absence of any constraint at the hip and knee joints and the presence of foot

platforms which movement simulates the phases of the gait cycle (Hesse et al., 2010). Among the exoskeleton systems we find the "LOPES" (Veneman et al., 2005) and the "Lokomat" (Colombo et al., 2000). This kind of devices can be considered as "fixed" robotic gait orthosis that move the patient's lower limbs miming the gait kinematics by acting at hip and knee level (Hesse et al., 2010). The comparison of end-effector and exoskeleton devices in a systematic review (Mehrholz and Pohl, 2012) suggested that post-stroke walking recovery may depend on the type of robotic device, even if the lack or a direct comparison between the two typologies of device make difficult to base a final clinical recommendation.

2.9.1 Current evidence from clinical trials

Although a set of data does not support a clear benefit of robotic gait training when compared with therapist-assisted one (Hidler et al., 2005; Hornby et al., 2008) and the matter is still disputed, several publications Whighlighted that robotic gait training is at least equivalent to therapist-assisted treadmill training in terms of efficacy and that electromechanical driven gait rehabilitation leads to a more symmetric gait pattern, to a lower spasticity and a more physiologic gait kinematics (estlake and Patten, 2009) Mayr et al., 2007). Nevertheless, despite the fact that robotic gait rehabilitation is paving the way for a substantial improvement of rehabilitation deliver, the way by which they determine restoration of function has not been yet clarified and the neurophysiological mechanisms underlying the recovery is still undefined.

2.9.2 Examples of devices

Lokomat

The Lokomat (Hocoma) is the most widely studied robotic gait training device on the market. This work-station device consists of a treadmill, a body weight support system, and bilateral exoskeletal components, which provide actuation at the hips and knees. Optional elastic foot lifters provide additional support at the ankle if needed. The Lokomat software supports a range of "guidance" parameters. At its maximal level, the device guides the limbs through a predefined movement pattern, established by studies of normal gait. As guidance is reduced, the device permits increased deviation from this trajectory before providing assistance [ref]. The afferent feedback is stimulation the re-organization of the CNS. Key features are active participation and motivation of the patient.

G-EO system

The G-EO System Robot (Reha Technologies) is a commercially available, end-effector system developed specifically for stroke rehabilitation. The device is conceptually similar to an elliptical machine, with two footplates that move along a designated path, in addition to a body weight support system. The device senses a patient's effort to move and responds by producing the prescribed gait pattern. It also offers a Partial Movement mode, which enables isolation and repetition of gait components. The G-EO enables customization of ambulation parameters such as step length, step height, and foot angles during toe off and initial contact.

Wearable devices

ReWalk

A specific rehabilitation robotics for gait support is the ReWalk device. ReWalk, initially proposed for spinal injured people, is a new realization of the powered exoskeleton concept and provides user-initiated mobility. It consists of a light wearable brace support suit, which integrates actuation motors at the joints, an array of motion sensors, a computer system based on sophisticated control and safety algorithms and tailored rechargeable batteries 10. This is a different kind of exoskeleton in which the control of the gait is made on the crutches. However, wheelchair remains the best solution because it's more stable and safer. The main problem of wheelchair is the immobility of the joint, which implies problems as demineralization, devascularization and risk of thrombosis. The idea of this exoskeleton is not to abandon the wheelchair, but to train the subject for an hour and to be used during some important events. ReWalk helps injured people to train in a non-boring way.

HAL

The Hybrid Assistive Limb (HAL) suit by Cyberdyne is a device originally developed for older adults with muscle weakness. The device has a modular design, which allows it to provide support unilaterally or bilaterally at the hip and/or knee. The hybrid system supports autonomous control, driven by weight shift, or voluntary control, driven by activation of specific muscles, as determined by surface EMG.

2.10 Soft Robotics

One of the emerging sectors of bio-robotics that can be a turning point for the development of portable devices, allowing home therapies (reducing in this way overall rehabilitation costs) and, at the same time, improving daily activities, is the soft

robotics. It invests in soft and flexible materials to make wearable devices inspired by nature and able to interact more safely with humans and the external environment, in order to overcome the problem of large dimensions and volumes of traditional robotic devices. As explained by [43], the lack of rigid components removes constraints on non-actuated degrees of freedom and also reduces joint alignment issues, which could prevent joint damage. Soft robotic devices, developed for rehabilitation purposes for most major joints of the body, include the ankle, knees, shoulder, elbows and wrists. There is also a slower trend, within the research in soft robotics, towards the development of devices that integrate one or more feedback modalities to detect the user's intention, accompanied by robotic augmentation of that intent. These feedback modalities include bend and pressure sensors on the digits or wrist, electroencephalography readings, surface electromyography readings and voice activation. This could lead to a further improvement of the rehabilitation process [43].

2.11 Conclusions

The level of evidence and the consequent strength of recommendations about the use of robotic devices can be drawn according to the American Heart Association, as shown in Fig. 2.3 [8].

To draw a conclusion, the impact of robot-assisted training is still debated: it guarantees intensive, repeatable, task-specific training, but up to now it seems an implementation to rather than a replacement for conventional physical therapy. Randomized controlled trials with large sample of patients are needed to draw more defined conclusions. A precise analysis of the economic burden and of the effectiveness of robotic rehabilitation is required. In this perspective, a better understanding of the central mechanisms underlying both spontaneous and training-guided recovery becomes mandatory in order to maximally take advantage from the brain capacity to reorganize its neural networks after damage. The neural mechanisms underlying the possible improvement led by robot-based therapeutic approach are still unclear, although recent studies have begun to shed light on this topic, trying to make the most of the phenomenon of brain plasticity in order to achieve the ultimate goal of reconnecting "intention" to "action" [44]). An improved knowledge of these neural processes could help to ameliorate the effectiveness of the robotic therapy, and design combined protocols, i.e., robot-based and plasticizing therapy, able to boost the functional motor recovery. Further studies will allow a better understanding of the effect of rehabilitation on neural plasticity in order to adapt treatment resources to meet the needs of each patient and optimize the recovery process. In this context, animal models can be a suitable solution to investigate neural and motor changes after stroke and

possible rehabilitative strategies, allowing the integration of behavioral, molecular and electrophysiological data.

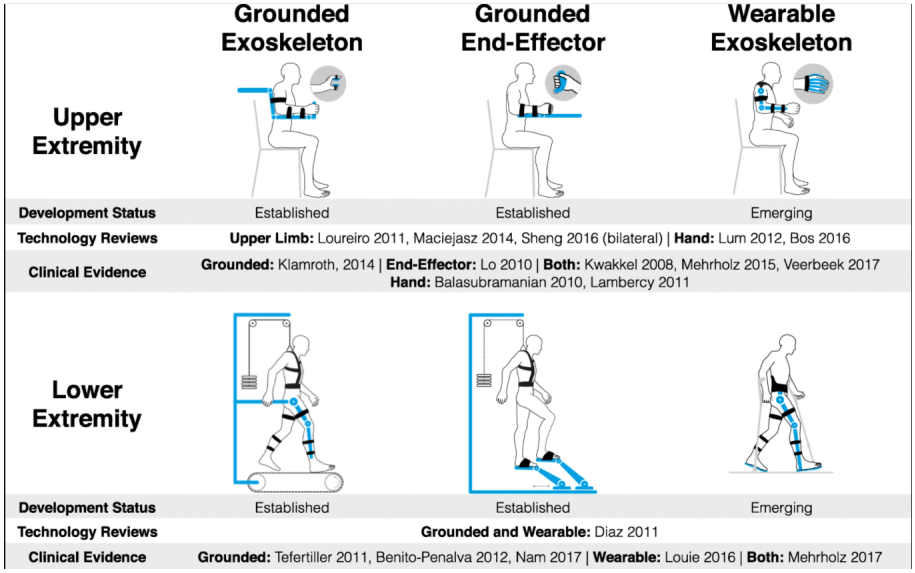

Figure 2.2: *Classification of rehabilitative robotic devices [29].*

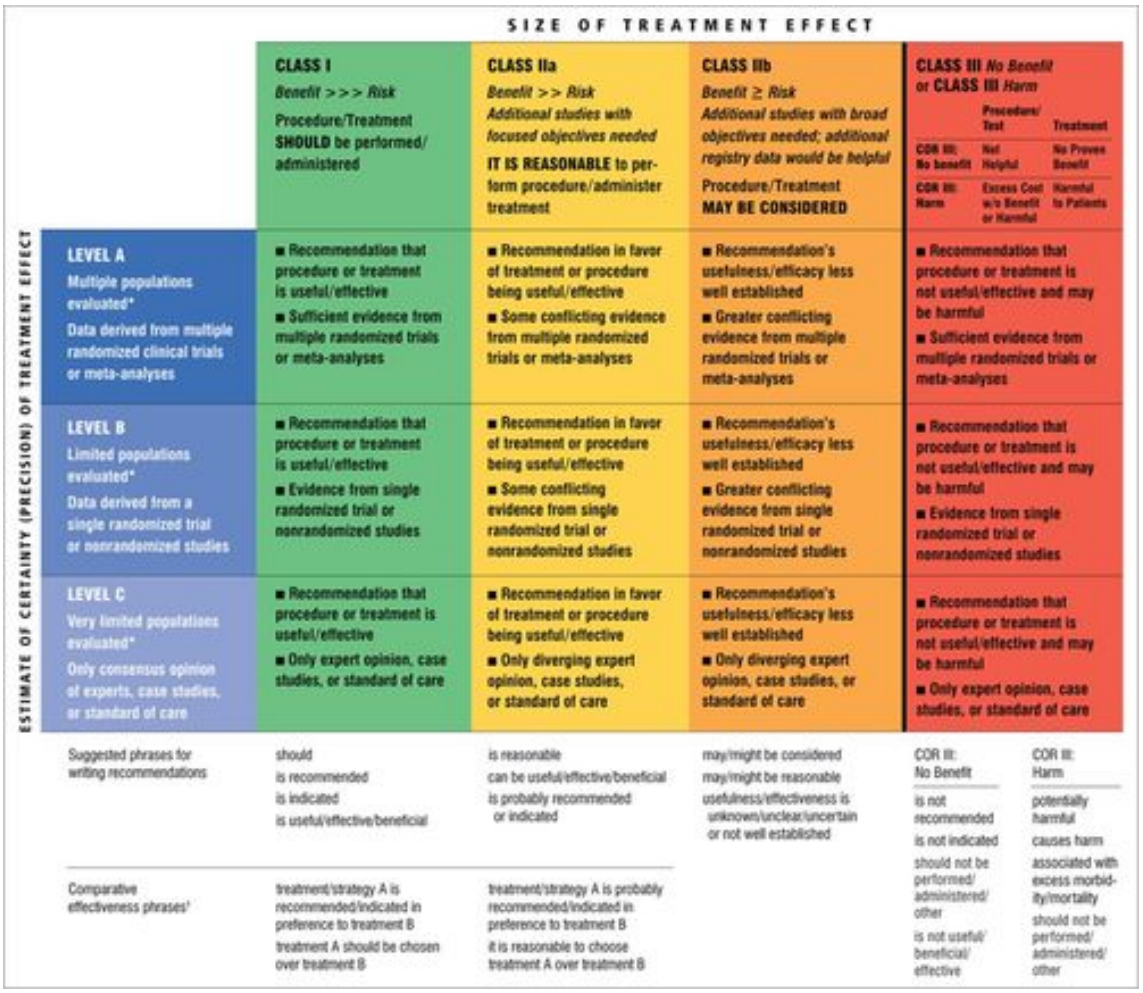

Figure 2.3: *Applying Classification of Recommendations and Level of Evidence [8].*

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