The three laws of Neurorobotics: a review on what neurorehabilitation robots should do for patients and clinicians

Iosa Marco, Morone Giovanni, Andrea Cherubini, Paolucci Stefano

The three laws of Neurorobotics: a review on what neurorehabilitation robots should do for patients and clinicians

Iosa Marco, PhD[1], Morone Giovanni, MD[1], Andrea Cherubini, PhD[2], Paolucci Stefano, MD[1].

[1] *IRCCS Fondazione Santa Lucia, Rome, Italy*

[2] *CNRS-UM LIRMM UMR 5506, IDH group, 161 Rue Ada, 34392, Montpellier, France*

Running Head: The three laws of neurorobotics

Corresponding Author:

Marco Iosa

Clinical Laboratory of Experimental Neurorehabilitation,

Fondazione Santa Lucia I.R.C.C.S.

Via Ardeatina 306, 00179 Roma

Ph: +39-06-51501077

Fax: +39-06-51501004

Email: m.iosa@hsantalucia.it

Abstract

Most of the studies and reviews on robots for neurorehabilitation focus on their effectiveness, giving controversial results. This and many other reasons concur to limit the credit given to these robots by therapists and patients. Further, neurorehabilitation is often still based on therapists' expertise, with competition among different schools of thought, generating substantial uncertainty about what exactly a neurorehabilitation robot should do. Conversely, poor attention has been deserved to ethics. This review adopts a new approach, inspired by Asimov's three laws of robotics and based on the most recent studies in neurorobotics, for proposing new guidelines for designing and using robots for neurorehabilitation. We propose three laws of neurorobotics based on: the ethical need of safe and effective robots, the redefinition of their role as therapist helpers, and the need for clear and transparent human-machine interfaces. These laws may allow engineers and clinicians to work closely together at a new generation of neurorobots.

Keywords: Rehabilitation, robotic training, neuroscience, ethics, medical robots

Introduction

The controversial effectiveness of robots for neurorehabilitation

The first robots appeared in neurorehabilitation in the eighties [1,2], their amusing potentialities were claimed in the nineties [3-5], and robotic exoskeletons started to spread in the nineties [6-7]. However, the debate on the effectiveness of robots in neurorehabilitation, is still an open question.

Contrasting results were obtained in different studies about neurorehabilitation robot efficacy [8-11], despite some randomized controlled trials performed on wide samples reported significant improvements in the outcome of robot-assisted therapy with respect to usual care [12, 13]. Meta-analyses have only partially helped in clarifying if there is an objective effectiveness of robotic training, being most results not conclusive. A 2008 Cochrane review on post-stroke arm training robots [14] concluded its analysis on 11 studies (328 subjects) stating that: “patients who receive electromechanical and robot-assisted arm training after stroke are not more likely to improve their activities of daily living, but arm motor function and strength of the paretic arm may improve”. The same authors further updated their Cochrane review in 2012 [15], including 19 trials (666 subjects), concluding: “Patients who receive electromechanical and robot-assisted arm training after stroke are more likely to improve their generic activities of daily living. Paretic arm function may also improve, but not arm muscle strength”. These results were hence in opposition with those obtained previously. Despite the second Cochrane should be considered more reliable, given the higher number of trials and enrolled subjects, the contrasting results (also in terms of muscle strength) lead to confusion.

Cochrane reviews on walking rehabilitation performed using robots, also provide inconsistent results. A Cochrane review, as well as its update [16,17], reported higher probability of recovery in patients who receive electromechanical-assisted gait training in combination with physiotherapy, whereas another Cochrane review [18] reported similar recovery probabilities for patients with and without treadmill training (i.e., with and without body weight support).

Besides effectiveness, other three aspects deserved attention. Firstly, these Cochrane reviews analysed electromechanical devices and robots as a single and homogeneous field. In fact, electromechanical devices developed for neurorehabilitation, e.g.: treadmill with body weight support or Gait Trainer (Reha-Stim, Berlin), are often but improperly considered members of the robot family [19]. This is a major concern for the designers of robot-therapy systems, who have failed so far to provide a comprehensive and agreed framework for the correct classification of these devices [20]. A second aspect deserving attention is that many studies about the efficacy of specific devices were published after their commercialization. This approach is inconceivable in other medical fields, for example pharmacology. The third point to take into account is that effectiveness should be referred not only to the device per se, but also to the specific patient groups targeted by the therapy [21-23], and to the timing and protocol adopted for that device [24]. This point was already highlighted by Mehrholz and colleagues [16]: the correct use of new technologies must rely on the information regarding the types of patients and the phase of rehabilitation that will benefit from specific technologies. For example, patients with more severe impairments in the motor leg can benefit more from robotic-assisted therapy, in combination with conventional therapy, than from conventional therapy alone. This likely occurs because, in the case of very impaired patients, robotic devices, increase the therapy intensity with respect to conventional ones [21,22]. Conversely, patients with greater voluntary motor function in the affected limb can perform intensive training also in conventional therapy. For these patients, neurorehabilitators may prefer less constrained, more ecological and more variable exercises [25]. Physical conditions are not the only ones to play a fundamental role in determining the best class of neurorobots users: the patient psychological profile can also be important in attaining superior motor outcomes with robot training than with conventional therapy [24].

These results lead to propose a change in the research question about the effectiveness of robot devices: "instead of asking ourselves whether robotic devices are effective in rehabilitation, we should determine who will benefit more from robotic rehabilitation" [25]. Inclusion and exclusion criteria are not the only characteristics to be determined in the design of a rehabilitation protocol when a robot is used. Few studies have focused on the definition of guidelines for an effective selection of movement parameter values (such as joint angles, speeds, applied forces and torques, etc.) and for better timing of robot therapy administration, both tailored on the patient's capacities and needs.

However, before further discussing the issue of effectiveness, and the reasons of the limited credit that is given to neurorobots, it is fundamental to clarify the difference between robots and electromechanical devices, defining what a neurorobot is.

What is a neurorobot?

Some cooking machines are commonly called robots by manufacturers and end-users. However, no one calls robot a mixer. This does not depend on the machine complexity: a car is usually more sophisticated than a cooking machine, but no one considers cars to be robots. On the contrary, clinicians and sometimes neuroscientists often confound electromechanical devices with robots [20].

The word "robot" appeared for the first time in 1921 in a science fiction play titled R.U.R. (Rossum's Universal Robots) written by the czech author Karel Capek. It derives from the Czech word “robota”, meaning forced workers, serf labors [19,26]. The robots invented by Capek were not robots in the popularly understood sense of mechanical devices, but they were assembled biological organisms. However, the term has since come to signify primarily electromechanical devices (often humanoid) endowed with artificial intelligence and able to perform a variety of functions, partly through programming and partly through their own ability to act autonomously [27]. According to that, the Robot Institute of America defined a robot as “a programmable, multi-functional manipulator designed to move material, parts or specialized devices through variable programmed motions for the performance of a variety of tasks” [28].

The expression neurorobotics, usually indicates the branch of science combining neuroscience, robotics and artificial intelligence. It hence refers to all the robots developed for interacting with or for emulating the nervous system of humans or other animals. A neurorobot can be developed for clinical purposes, for example neurorehabilitation or neurosurgery, or for studying the nervous system by emulating its properties, as it occurs for example in the walking robots based on central pattern generators [29].

As mentioned above, a robot should be capable of performing a variety of tasks. This adaptability is based on its on-board sensors, the signal of which are processed by an artificial intelligence, to properly change the behaviour of robot. Hence, the fundamental point differentiating robots from electromechanical devices is the adaptability of their operation. In neurorehabilitation, this differentiation has often been considered as picky, and robots and electro-mechanical devices were often associated during analyses of their efficacy [19]. Treadmills with body weight support and other devices such as the Gait Trainer (Reha-Stim, Berlin) should be defined as electromechanical devices, because, once the physiotherapist has fixed their parameters, they are not capable of autonomously adapting them during operation. Conversely, other devices developed for walking recovery, such as the Lokomat (Hocoma, Volketswil) can be defined as robots since they use sensors to adapt their functioning to the patient’s performance (e.g., the Lokomat has a position control mode for applying an assistance-as-needed guidance force to the lower limbs).

Features of neurorehabilitation robots

Many neurorehabilitation approaches and techniques have been developed to restore neuromotor function aiming at the recovery of physiological movement patterns in patients with neurological pathologies. But none has emerged as a gold standard, since it is a common opinion that methods should be specifically tailored for pathologies and patients [30]. However, a common feature of the different neurorehabilitative approaches is the need for intensive, repetitive and task-oriented treatments [25].

Many authors reported that robots could improve rehabilitation outcome, in accordance with such feature. In 2008, Wolbrecht and colleagues [31] identified the three main desirable features for a controller of robot-aided movement training. One year later, Morasso et al. [20] re-elaborated these features, adding the importance of haptic properties and auto-adaptive capacities. Then, Belda-Lois and colleagues [30] suggested four different features for favouring a top-down approach when a robot is used for post-stroke gait recovery. Finally, Dietz et al. [32] reported four main potential advantages in the use of robots in neurorehabilitation. All these features are recalled in Table 1.

The features indicated by Wolbrecht and colleagues [31] mainly focused on the need of adaptability of neurorobots to the different patients' abilities. Morasso et al. [20] added that a robot must have also haptic properties and some intelligent capabilities related to an adaptive assist-as-needed approach. Both studies highlighted the importance of a high mechanical compliance, i.e. the need of having a robot with a low-stiffness control. A stiff position controller, as that of industrial robots, could move the limbs along the desired trajectories limiting the errors. However, such a controller impedes error-based learning, that is an essential component of motor re-learning [20]. Furthermore, a low-stiffness robot is potentially less dangerous than a high-stiffness robot in the interaction with the patient [20]. The other two references [30,32] were more related to the importance of intensive (for patients and not for therapists) and repeatable exercises. Both also pointed out the possibility of exploiting the robot sensors not only to adapt to the patient's performance, but also to provide biofeedback to the patient (increasing his/her motivation and hence participation to rehabilitation), and feedback to therapists and clinicians on the patient progressions. It should be noted as no-one of these features claims for effectiveness, probably because it is taken for granted when training is performed in a patient-tailored, intensive, repetitive and task-oriented manner, but this issue should deserve further attention.

The effectiveness paradox in neurorobotics

Morasso and colleagues noted a paradox in the assessment of effectiveness of neurorehabilitation robots [20]. Most of the studies agree in suggesting that robotic treatment should be highly personalized, by setting the robot parameters in order to exploit the residual capabilities of each patient for recovering a functional status. This implies that in order to be effective, robotic treatment cannot be standardized, and therefore controlled clinical trials in the traditional sense are impossible, unless aimed at very specific and narrow groups (implying small sample size, hence poor statistical evidence). The contrast between a standardized treatment (with clear guidelines) allowing the design of randomized controlled trial (and of clear rehabilitative programmes) with an adaptable treatment, tailored for patients' capabilities, is the core of this effectiveness paradox.

Furthermore, the contrast between standardization and adaptability is not the only opposition to a univocal approach. An intensive training may increase the risk of inducing or augmenting spasticity. Besides, the monotony of the same exercise with identical trajectories clashes with the need of continuous adaptation of robots to the changing abilities of patients and with the need for motivating rather than boring exercises. Finally, most of the robots help patients in reproducing a movement replicating the physiological one, despite most severely affected patients have few possibilities of a complete recovery.

It can be noted that these controversies are present also in conventional neurorehabilitation training. The scientific bases of neuromotor physiology, neurorehabilitation and brain plasticity are still not completely clear. Neurorehabilitation is still mainly ill-defined, with competing schools of thought about the best treatment.

This generates another scientific roadblock for neurorobots. In fact, neither the optimal movement tasks, nor the optimal mechanical inputs, are well known. Therefore, the first problem that a robotics engineer encounters when setting out to build a robotic therapy device is that there is still substantial uncertainty as to what exactly the device should do [33], despite the above cited general features suggested in the literature.

Interestingly, the scepticism related to neurorobotics due to the rather inconclusive evaluation of its efficacy and to the above reported controversies, is not mitigated by the consideration that quite similar evaluations could be formulated for the variety of human-delivered rehabilitation techniques [20]. Thus, the doubts about the use of neurorobots could be not only imputable to the uncertainty related to efficacy, but also to some other barriers limiting their wider adoption in rehabilitative settings.

Other barriers limiting neurorobotics

Other aspects limiting neurorobotics are due to technological, behavioural and economical barriers [34]. Initial economic burden is surely a potential limit for the robot diffusion in neurorehabilitation, although it has been reported that the long-term use of neurorobots can decrease health-care system costs [20]. For example, a single physiotherapist could manage up to four robots (hence, four patients) at the same time [25]. Masiero and colleagues [35] quantified the cost of using NeReBot (a robot for the treatment of poststroke upper limb impairment) to be 37% of hourly physiotherapy cost, with benefits including the reduction of hospitalization time,. This suggests that robotic technology can be a valuable, and economically sustainable aid, in the management of patient rehabilitation. Hesse and colleagues found a similar percentage (41%), under the assumption that the therapist is needed only at the beginning and end of therapy, and in particular situations where help is needed. In general, rigorous studies on the economic sustainability of robots for neurorehabilitation are very sporadic [37]. These few studies suggest that robotic therapy may imply a reduction of costs for the healthcare system, in terms of reduction of hospitalization for each patient, and/or of higher autonomy at discharge. However, as interestingly highlighted by Turchetti and colleagues [37], the single hospital could be less interested than the final payer (e.g., the health national or local system, the private patient, or the insurance companies) to these aspects. However, this clearly depends on the reimbursement regimen and on the agreement between the parts. In general, uncertainty remains about the cost-effectiveness of robotic neurorehabilitation [38].

Technological and behavioural aspects could be related to the possibility that the expectations of patients and clinicians about outcomes of a neurorobotic treatment are too high with regards to the current biomedical engineering level. These reasons seem conceivable, but raise another question: why have not they limited other kind of medical robots, such as surgical ones? In fact, although the latter have been introduced in the nineties, just as neurorehabilitation robots, their benefit in assisting surgery (and especially minimally invasive surgery) is established. Even in fields with no unequivocal evidence of the superiority of robot-assisted over traditional surgery, the popularity and diffusion of robotic surgery has progressively increased [39], up to the statement that, in the last 25 years, robots have brought a tremendous improvement to the field of surgery [40]. Thus, other reasons should be investigated to deeply understand what still lacks to neurorehabilitation robots in order to match the patients and clinicians expectations. And in this scenario, an irrational aspect seems to play a fundamental role.

Fear of robots

In the play of Capek, robots are initially obedient, and, when commanded, they perform the required task, by literally following the human instructions. Then, they substitute humans in their works, and finally they escape human control and start a rebellion. This theme was similar to the previously existent Jewish myth of the Golem of Prague (an animated anthropomorphic being entirely created from inanimate matter) and was further present in many science fiction works. Could fear actually play a role in the scepticisms on neurorobots?

In general, the studies that performed questionnaires to collect the opinions of users (patients and therapists) of neurorehabilitation robots, reported a good usability, comfort, acceptability and satisfaction. However, most were feasibility studies enrolling healthy subjects [41], less than 10 patients [42-46], or lacking a control group undergoing conventional physiotherapy [47,48]. Even when the control group was present, only the satisfaction of experimental physiotherapy was assessed [49]. Hence, these positive results should be read with caution, since they have been obtained on a small group of users, often not randomly assigned to robotic therapy. Furthermore, these results can generate a bias, since the patients, who accepted to participate to robotic therapy, could be the more trustful with regards to the use of new technological rehabilitation interventions.

In 2000, Burgar and colleagues, in a study reporting their experience in developing robots for neurorehabilitation, had to drastically conclude their work stating “we do not view robots as replacements for therapists” [50]. However, most of the initial studies on robots claimed that robotic devices can reduce the number of therapists and the associated costs needed for rehabilitation [25, 51,52] (despite there are also cases in which two physiotherapists are required for preparing the most severely affected patients to robotic neurorehabilitation: this is typically the case when harnessing the patient on robots for walking recovery based on body weight support [24]).

Furthermore, in terms of control, the patient’s feelings related to robot use in neurorehabilitation should also be considered. Bragoni and colleagues [23] identified the level of anxiety of patients as a negative prognostic factor for robotic therapy and not for conventional therapy. On the contrary, patients who saw themselves as chief causal factor in managing their recovery, showed higher probability of a better outcome of robotic rehabilitation [23]. This kind of fear could be due to the sensation that robots are not considered trustworthy because lacking of human feelings, expertise and commonsense [52]. This is notoriously one of the hardest problems in artificial intelligence and robotics, faced nowadays by bioengineers, just as it was faced by science fiction writers, in the past.

The three laws of Neurorobotics

The three laws of Robotics

After the play of Capek, robots became one of the iconic staples of humans’ imagination, especially thanks to Isaac Asimov’s stories, and to his compilation “I, Robot” of 1950 [53]. In a story included in that compilation and first published in 1942 titled “Runaround”, Asimov invented the three laws of robotics quoted as being from the "Handbook of Robotics, 56th Edition, 2058”. These rules are a set of fundamental requirements for the design and manufacture of intelligent robots. They are intended to ensure that robots will operate for the benefit of humanity, rather than becoming a threat to humans. These laws had a very influential role in the following science fiction works, and became also important with the emergence of robotics as a scientific discipline [54]. The three laws of robotics are:

1) A robot may not injure a human being or, through inaction, allow a human being to come to harm.

2) A robot must obey the orders given it by human beings, except where such orders would conflict with the First Law.

3) A robot must protect its own existence, as long as such protection does not conflict with the First or Second Laws.

These laws define a kind of set of ethic rules for robots (or for the human programmers of their artificial intelligences). The hierarchical structure of these laws put at the first level human health, followed by human will, and finally robot self-safeguard. These laws should not be considered only as part of science fiction imagery. Their potential role is so important, that they have been re-analyzed in the current context, within the Editorial of a Special Issue of Science, entitled "Robot Ethics" [55]. In this editorial, Sawyer stated that, since the U.S. military is a major source of funding for robotic research, it is unlikely that such laws will be integrated in their design. This argument can be generalized to cover other robotic industries: the development of artificial intelligence is a business, and businesses are usually uninterested in ethical issues. The risk, in the neurorehabilitation field, is that companies may produce attractive robots without proving their effectiveness. The potential risks related to the use of medical robotics deserve attention: harms may occur for anomalous functioning, but harmful events may even be caused by normal robot behaviour [52]. If many of the problems related to neurorobots are related to fear, risks and ethical issues, it is probably time to define a set of rules also for neurorobot ethics, before defining their desirable features.

The three laws of Neurorobotics

According to the aforementioned desirable features of a neurorobot, we have re-formulated the three laws of robotics into three laws for robotics in neurorehabilitation, and we will further discuss their meanings and implications:

1) A robot for neurorehabilitation may not injure a patient or allow a patient to come to harm.
2) A robot must obey the orders given it by therapists, except where such orders would conflict with the First Law.
3) A robot must adapt its behavior to patients' abilities in a transparent manner as long as this does not conflict with the First or Second law.

Discussion

The first law of neurorobotics: the need of a high benefit/risk ratio

Personal care robots, i.e. mobile servant robots, physical assistant robots and person carrier robots, should be designed in accordance in accordance with the international standards defined by ISO 13482:2014 [56]. Only in 2014 the International Organization for Standardization published these criteria for designing personal care robots, providing the needed requirements to eliminate or reduce the risks associated with the use of medial robots to an acceptable level. The ISO 13482:2014 is more specific for personal care robots, including neurorobots, than the previous ISO14971:2000 [57]. The ISO 13482:2014 can be considered in line with the first law of Asimov. We should just specify that the expression “harm” should be intended as damage the patient. As shown by Datteri [52], in his interesting review about responsibility in using medical robots (including surgery and diagnostic robots, neurorehabilitation robots, robotic prostheses, and even next-generation personal assistance robots), these devices operate in close proximity or direct physical contact with humans, manipulate instruments inside the patient’s body or directly move user’s impaired limbs, and have invasive or non-invasive connections with the human nervous system. They can hence contribute to improving the precision of medical treatments, to relieving therapists of tasks, which require considerable accuracy and physical efforts, and to improving the quality of life of patients, as well as their ability to participate in social activities [59]. Nevertheless, they also may threaten the physical integrity of patients, not only through harmful events caused by anomalous behaviours (e.g., in surgery), but even through normal operation [52]. This can typically occur for neurorehabilitation robots, when their efficacy has not been proved [52]. That review reports the example of Lokomat, showing that, despite its diffusion in many rehabilitation centres, neither a well-supported experimental nor theoretical grounds have determined whether Lokomat-based therapies are at least as beneficial as conventional therapies. Instead, the same work, reports studies showing that Lokomat reproduces abnormal and non-physiological gait patterns due to the restriction of pelvis movement, altering lower limb joint kinematics [59] and muscle activations [60]. This limitation has recently been overcome in the Lokomat®Pro (Hocoma) by the adjunction of an optional module allowing lateral translation and transverse rotation of the pelvis, aiming at a more physiological movement. However, it is still unclear if a training based on physiological movement is the optimal solution also for patients severely affected and probably unable to completely recover physiological patterns. In fact, it should be kept clear in mind that recovery of autonomy in walking should be the objective of robotic gait rehabilitation, whereas recovery of physiological gait patterns is not mandatory.

Neurorobots should be safe not only in terms of movement, but also from other medical point of views. For example, in spite of the variety of gait patterns, the robotic gait training performed with body weight support has only recently proved safe for training intensive walk in non-autonomous ambulatory patients with subacute stroke. The reason is that the cardio-respiratory demand is lower than in conventional walk training performed overground [61]. Interestingly, authors found an opposite result in healthy subjects: overground walking was less demanding than robotic walking. They suggested that it could have been because the robot imposes non-natural trajectories, which force subjects to activate non-natural sensorimotor walking patterns.

However, we would like to enlarge the meaning of “harm” to all possible damage for patients. Time spent on an ineffective, poorly effective or even detrimental robot should be considered as damage, because the patient could spend the same time in a more effective treatment. Hence, the first law implies that a robot usage should be at least as safe and effective as other treatments, meaning that it should have a higher benefit-risk ratio than human administered treatments. This ratio should be evaluated before commercialization of the device, and not afterwards as nowadays often occurs.

But how can a robot be effective in the light of the cited effectiveness paradox and in the absence of a clear scientific background? Firstly, it is probably time to condition the commercial launch of neurorobots to a deep examination of their potential effectiveness, adopting an approach more similar to that used in other medical or engineering disciplines. For example, specific rules are defined for clinical trials prior to drug commercialization (Table 2). These trials require a Phase I, (commonly performed in the producer laboratories), followed by Phase II and III (performed in independent hospitals), before commercialization can occur. Further, a Phase IV follows in clinical or daily living settings. Dobkin redefined these phases for motor rehabilitation treatments [62] (again refer to Table 2), and we suggest that a similar roadmap should be followed by companies before commercialization of neurorobots (that should occur only after an equivalent phase III).

Furthermore, the handbooks of neurorehabilitation robots are at the moment still similar to generic commercial pamphlets, far from drug information sheets. The latter usually report indications, proper use, dosages, precautions, possible side effects, etc. In fact, the effectiveness of a treatment (including a treatment with a neurorehabilitation robot) depends on the patient characteristics (e.g., type and severity of disease, presence of specific deficits) [16], on the dose to administer, and on the correct phase of rehabilitation at which the therapy should be administered [25]. For example, Morone and colleagues reported that patients with more severe impairments in the motor leg benefited more from robotic-assisted therapy, than patients with greater voluntary motor function in the affected limb that can perform intensive and less constrained training in conventional therapy [21,22].

The second law of neurorobotics: a tool in the hands of therapists

As above reported, some therapists see a robot as a possible substitute of their work. No wonder Morasso and colleagues titled their review on robots for rehabilitation “Desirable features of a “humanoid” robot-therapist” [20]. Hidler and colleagues emphasized that the goal of introducing robots into rehabilitation hospitals is not to replace therapists, but rather that robots complement existing treatment options [51]. Nevertheless, it is reasonable to believe that the reduction of health care costs is at least one of the main motives driving research in neurorobotics [52], given the many studies reporting that robots may reduce the cost of rehabilitation by reducing the number of the required therapists [25,51,52].

Likely, the better popularity gained in recent years by neurosurgery robots, as compared to neurorehabilitation ones, is due to the fact the former do not replace the surgeon, but aid him by augmenting his hands stability and visual capacities. Similarly, a robot for rehabilitation should not be considered as a standing-alone rehabilitation device [63], but a tool in the hand of therapists, giving them more precise movements, more intensive, repeatable or adaptable patterns, according to the therapists’ expertise, and relieving them from fatigue. The therapist should therefore be included in the loop, in order to drive the symbiotic equilibrium between robot and patient towards an optimum, by dialoguing with the patient, motivating him/her, and getting verbal feedback on fatigue, pain and emotional stress (parameters difficult to be monitored with sensors) [52]. Recently, the need of therapist as motivator for avoiding a passive role of patient during robotic therapy has been overcome by the new top-down approach of recent robots combined with stimulating biofeedback, video-game based therapy, and even with brain computer interfaces [19, 30]. However, therapist should play a key role in terms of robotic therapy administration such as robot parameter adjustments, avoiding harmful patients’ compensation strategies, identification of the trade-off between challenging tasks for favuring rehabilitation and demoralising too difficult tasks.

To this end, we propose to extend the loop proposed by Morasso and colleague [20], to include the therapist (see Figure 1). In our opinion, the desired reduction of costs for health care system can be obtained not reducing the number of therapists, but increasing the efficacy of rehabilitation, reducing the length of stay in rehabilitative hospitals, and dismissing more autonomous patients with a consequent reduction of home care costs.

The proposed second law of neurorobotics, making the robot perfectly obedient to the therapists’ requests, may seem obvious, but it is not. Beside the above-described problems related to not-physiological gait patterns in Lokomat therapy [52], another evident example of robot “disobedience” is in the discrepancy between the desired and actual values of some parameters of the electromechanical Gait Trainer (as highlighted in [24]). The effective percentage of body weight supported by the machine resulted different from that selected in the initial static condition, since the machine does not take into account the changes occurred in the patient capacity to support his/her own weight during training. Furthermore, the authors highlighted that in the Gait Trainer, the defined selector of walking speed is actually a selector of step duration, and the reported speed coincides with the real one only if the maximum step length has been also selected.

Robots should “disobey” clinicians’ orders only if their sensors highlight that a potential risk for the patient can be provoked by that order. This highlights the importance of sensors, which is at the base of the adaptability and autonomy of any robotic system [28]. In contrast, an electromechanical device is not required to detect a potentially dangerous choice of therapists, due to wrong parameter tuning.

The third law of neurorobotics: artificial intelligence as a support for human intelligence

The presence of a therapist in the loop (Figure 1) allows human control of the device, but the robot’s artificial intelligence should not be limited to the safety control of human decisions. During rehabilitation, there are many parameters to calibrate, to tune and to adapt. Firstly, the clinician should always consider the effects of a parameter change on the other ones. For example, to increase speed during overground walking, a subject can reduce step duration and/or increase step length (usually both at the same time). In Lokomat training, when a therapist increases the patient’s walking speed, he/she is actually reducing the step duration, without altering the step length, since this parameter depends on the sagittal range of hip motion, and in the Lokomat changes in that range need a manual adjustment by the therapist. The handbook of Hocoma [64] suggests therapists to consider the following points when increasing the speed: 1) adapt step length by their intervention on hip range of motion; 2) adjust the synchronization between treadmill and exoskeleton speed (automatic setting is also possible); 3) adjust the hip offset (not only range); 4) take into account that foot impact could increase, and hence over-solicit the joints; 5) check the quality of the movement that may be affected by the change. This highlights how many parameters are related to a simple change of speed in a robot for gait training. Furthermore, speed is a parameter with a very clear physiological meaning. More problems could occur for a parameter for which is not so easy to understand the role, such as guidance force.

The robot artificial intelligence should be capable of automatically performing all the control changes required by the therapist, while providing him/her with a clear quantitative overview of all these changes. In fact, neurorobots have the potential for accurate assessment of motor function in order to assess the patient status, to measure therapy progress, or to give the patient and therapist real-time feedback on the movement performance [65]. This novel approach has been proposed in some recent studies. Kinematic robotic measures, especially those related to the range of motion, have recently been indicated as useful, in the assessment of motor deficits in reaching movements [66], and of proprioceptive function of hand [67], upper [68] and lower [69] limbs. Furthermore, kinetic robotic measures have been reported as useful in the assessment of upper limb strength [65]. The adoption of robotic technologies for helping patients and therapists and quantitatively evaluating the patient recovery is the main issue also of European projects, such as the MAAT ("Multimodal interfaces to improve therapeutic outcomes in robot-assisted rehabilitation") and SYMBITRON ("Symbiotic man-machine interactions in wearable exoskeletons to enhance mobility for paraplegics") projects. These projects include the patient in a symbiotic loop with the robot, similarly to what we have suggested in Figure 1. Then, the therapist should simply be required to qualitative control patient's performance under the new conditions.

Summarising these concepts: a new generation of human machine interfaces integrated in neurorobots should be developed, in which the therapist's commands at macro level can be translated in micro changes autonomously by robot that informed the therapist of these changes. However, there are no easy ways to assess algorithmically whether the robot performed self-adaptation (that actually is a mutual patient-robot adaptation) can be the optimal one for neuromotor recovery [52]. For this reason, the therapist should be kept into the loop, because of his/her skills, expertise, and common sense. In contrast with the robot, the therapist has a qualitative but natural access to the health status of the patient. For instance, he/she can have a detailed feedback of feelings and sensations, by just dialoguing with patient.

Conclusions

Most of the studies and reviews about robots for neurorehabilitation have focused on their effectiveness, but have found controversial results. Poor attention has been given to robot ethics, probably because the artificial intelligences on board are still primitive. However, data shows that patients and therapists are somewhat afraid of such robots. Although we have not suggested new technical solutions, in this review, we have described the state of the art of robots for neurorehabilitation, and suggested a set of rules to make a step over the actual limits and problems. This was done in an original manner, by reformulating, in the field of neurorobotics, the three laws of robotics depicted by Asimov in science fiction. We have motivated the need for these laws with many examples. The so obtained three laws of neurorobotics highlight the ethical need to prove the robots' effectiveness before their commercialization, as well as the desirable features that neurorobots should have. Furthermore, we highlight the need of including therapist into the loop between patient and robot, because of his/her fundamental role. Finally, we suggested that neurorobots can be a new valuable tool in therapists' hands, helping them not only in repetitive and intensive patients' mobilization, but also providing quantitative information about patient's deficits, residual abilities and functional recovery. We think that these three laws may bring together engineers and clinicians, for the development of a new, effective generation of robots for neurorehabilitation.

Conflict of interests
The authors declare that they have no conflict of interest.

References

1. Krebs, H.I., Hogan, N., Aisen, M.L., & Volpe, B.T. (1998). Robot-aided neurorehabilitation. IEEE Transactions on Rehabilitation Engineering, 6(1),75-87.
2. Gosine, R.G., Harwin, W.S., Furby, L.J., & Jackson, R.D. (1989). An intelligent end-effector for a rehabilitation robot. Journal of Medical Engineering & Technology, 13(1-2),37-43.
3. Preising, B., Hsia, T.C., & Mittelstadt, B. (1991). A literature review: robots in medicine. IEEE Engineering in Medicine and Biology Magazine, 10(2), 13-22.
4. Van Vliet, P., & Wing, A.M. (1991). A new challenge--robotics in the rehabilitation of the neurologically motor impaired. Physical Therapy, 71(1), 39-47.
5. Aisen, M.L., Krebs, H.I., Hogan, N., McDowell, F., Volpe, B.T. (1997). The effect of robot-assisted therapy and rehabilitative training on motor recovery following stroke. Archives of Neurology, 54(4), 443-446.
6. Hesse, S., Schmidt, H., Werner, C., Bardeleben, A. (2003). Upper and lower extremity robotic devices for rehabilitation and for studying motor control. Current Opinion in Neurology, 16(6), 705-710.
7. Veneman, J.F., Kruidhof, R., Hekman, E.E., Ekkelenkamp, R., Van Asseldonk, E.H., Van der Kooij, H. (2007). Design and evaluation of the LOPES exoskeleton robot for interactive gait rehabilitation. IEEE Transactions on Neural Systems & Rehabilitation Engineering, 15(3), 379-386.
8. Hidler, J., Nichols, D., Pelliccio, M., Brady, K., Campbell, D.D., Kahn, J.H., et al. (2009). Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. Neurorehabilitation and Neural Repair, 23: 5-13.

9. Husemann, B., Müller, F., Krewer, C., Heller, S., Koenig, E. (2007). Effects of locomotion training with assistance of a robot-driven gait orthosis in hemiparetic patients after stroke: a randomized controlled pilot study. Stroke, 38, 349-354.
10. Pohl, M., Werner, C., Holzgraefe, M., Kroczek, G., Mehrholz, J., Wingendorf, I. et al. (2007). Repetitive locomotor training and physiotherapy improve walking and basic activities of daily living after stroke: a single-blind, randomized multicentre trial (DEutsche GAngtrainerStudie, DEGAS). Clinical Rehabilitation, 21, 17-27.
11. Tong, R.K., Ng, M.F., & Li, L.S. (2006). Effectiveness of gait training using an electromechanical gait trainer, with and without functional electric stimulation, in subacute stroke: a randomized controlled trial. Archives of Physical & Medicine Rehabilitation, 87, 1298-1304.
12. Lo, A.C., Guarino, P.D., Richards, L.G., Haselkorn, J.K., Wittenberg, G.F., & Federman, D.G. (2010). Robot-assisted therapy for long-term upper-limb impairment after stroke. N Engl J Med. 362(19): 1772-1783.
13. Klamroth-Marganska, V., Blanco, J., Campen, K., Curt, A., Dietz, V., Ettlin, T., et al. (2014). Three-dimensional, task-specific robot therapy of the arm after stroke: a multicentre, parallel-group randomised trial. Lancet Neurol. 13(2):159-166.
14. Mehrholz, J., Platz, T., Kugler, J., Pohl, M. (2008). Electromechanical and robot-assisted arm training for improving arm function and activities of daily living after stroke. The Cochrane Database of Systematic Reviews, 8(4):CD006876.
15. Mehrholz, J., Hädrich, A., Platz, T., Kugler, J., Pohl, M. (2012). Electromechanical and robot-assisted arm training for improving generic activities of daily living, arm function, and arm muscle strength after stroke. The Cochrane Database of Systematic Reviews, 6:CD006876.
16. Mehrholz, J., Werner, C., Kugler, J., Pohl, M. (2007). Electromechanical-assisted training for walking after stroke. The Cochrane Database of Systematic Reviews. 4:CD006185.
17. Mehrholz, J., Elsner, B., Werner, C., Kugler, J., Pohl, M. (2013). Electromechanical-assisted training for walking after stroke. The Cochrane Database of Systematic Reviews. 7:CD006185.
18. Mehrholz, J., Pohl, M., Elsner, B. (2014). Treadmill training and body weight support for walking after stroke. The Cochrane Database of Systematic Reviews. 1:CD002840.
19. Iosa, M., Morone, G., Fusco, A., Bragoni, M., Coiro, P., Multari, M., et al. (2012) Seven capital devices for the future of stroke rehabilitation. Stroke Research & Treatment, 2012:187965.

20. Morasso, P., Casadio, M., Giannoni, P., Masia, L., Sanguineti, V., Squeri, et al. (2009). Desirable features of a "humanoid" robot-therapist. Conference proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2009:2418-21.
21. Morone, G., Bragoni, M., Iosa, M., De Angelis, D., Venturiero, V., Coiro, P., et al. (2011). Who may benefit from robotic-assisted gait training? A randomized clinical trial in patients with subacute stroke. Neurorehabilitation & Neural Repair, 25(7), 636-644.
22. Morone, G., Iosa, M., Bragoni, M., De Angelis, D., Venturiero, V., Coiro, P., et al. (2012). Who may have durable benefit from robotic gait training?: a 2-year follow-up randomized controlled trial in patients with subacute stroke. Stroke, 43(4), 1140-1142.
23. Bragoni, M., Broccoli, M., Iosa, M., Morone, G., De Angelis, D., Venturiero, V., et al. (2013). Influence of psychologic features on rehabilitation outcomes in patients with subacute stroke trained with robotic-aided walking therapy. American Journal of Physical & Medicine Rehabilitation, 92(10 Suppl 2):e16-25.
24. Iosa, M., Morone, G., Bragoni, M., De Angelis, D., Venturiero, V., Coiro, P., et al. (2011). Driving electromechanically assisted Gait Trainer for people with stroke. Journal of Rehabilitation Research & Development, 48(2), 135-146.
25. Masiero, S., Poli, P., Rosati, G., Zanotto, D., Iosa, M., Paolucci, S., et al. (2014). The value of robotic systems in stroke rehabilitation. Expert Review of Medical Devices, 11(2), 187-198.
26. Roberts, A. (2006). The History of Science Fiction. New York, NY: Palgrave MacMillan.
27. Keith Booker, M. (2015). Historical Dictionary of Science Fiction in Literature. Lanham, Maryland: Rowman & Littlefield.
28. Ming Xie (2003). Fundamental of Robotics: Linking Perception to Action. Singapore: World Scientific.
29. Ijspeert, A.J., Crespi, A., Ryczko, D., & Cabelguen, J.M. (2007). From swimming to walking with a salamander robot driven by a spinal cord model. Science, 315, 1416-1420.
30. Belda-Lois, J.M., Mena-del Horno, S., Bermejo-Bosch, I., Moreno, J.C., Pons, J.L., Farina, D., et al. (2011). Rehabilitation of gait after stroke: a review towards a top-down approach. Journal of Neuroengineering & Rehabilitation, 8:66.
31. Wolbrecht, E.T., Chan, V., Reinkensmeyer, D.J., & Bobrow, J.E. (2008). Optimizing compliant, model-based robotic assistance to promote neurorehabilitation. IEEE Transactions on Neural Systems & Rehabilitation Engineering, 16(3), 286-297.

32. Dietz, V., Nef, T., & Rymer, W.Z. (2012). Neurorehabilitation Technology. London, UK: Springer.
33. Van Der Loos, H.F.M., & Reinkensmeyer, D.J. (2008). Rehabilitation and health care robotics. In Siciliano B. & Khatib O. (Eds.), Springer Handbook of Robotics (pp. 1223–1251). Berlin, Heidelberg: Springer.
34. Turchetti, G., Vitiello, N., Trieste, L., Romiti, S., Geisler, E., & Micera, S. (2014). Why effectiveness of robot-mediated neurorehabilitation does not necessarily influence its adoption. IEEE Reviews in Biomedical Engineering, 7, 143-153.
35. Masiero, S., Poli, P., Armani, M., Ferlini, G., Rizzello, R., & Rosati, G. (2014). Robotic upper limb rehabilitation after acute stroke by NeReBot: evaluation of treatment costs. Biomed Res Int. 2014:265634.
36. Hesse, S., Heß, A., Werner, C., Kabbert, N., & Buschfort, R. (2014) Effect on arm function and cost of robot-assisted group therapy in subacute patients with stroke and a moderately to severely affected arm: a randomized controlled trial. Clin Rehabil. 28(7):637-647.
37. Turchetti, G., Vitiello, N., Trieste, L., Romiti, S., Geisler, E., & Micera, S. (2014), Why effectiveness of robot-mediated neurorehabilitation does not necessarily influence its adoption. IEEE Rev Biomed Eng. 7:143-53.
38. Wagner, T.H., Lo, A.C., Peduzzi, P., Bravata, D.M., Huang, G.D., Krebs, H.I., et al. (2011). An economic analysis of robot-assisted therapy for long-term upper-limb impairment after stroke. Stroke; 42(9):2630-2.
39. Ng, A.T., & Tam, P.C. (2014). Current status of robot-assisted surgery. Hong Kong Medical Journal, 20(3), 241-250.
40. Spetzger, U., Von Schilling, A., Winkler, G., Wahrburg, J., & König, A. (2013). The past, present and future of minimally invasive spine surgery: a review and speculative outlook. Minim Invasive Therapy & Allied Technologies, 22(4), 227-241.
41. del-Ama, A.J., Gil-Agudo, A., Pons, J.L., & Moreno, J.C. (2014). Hybrid FES-robot cooperative control of ambulatory gait rehabilitation exoskeleton. J Neuroeng Rehabil. 11:27.
42. Sale, P., Lombardi, V., & Franceschini, M. (2012). Hand robotics rehabilitation: feasibility and preliminary results of a robotic treatment in patients with hemiparesis. Stroke Res Treat. 2012:820931.
43. Vanmulken, D.A., Spooren, A.I., Bongers, H.M., & Seelen, H.A. (2015). Robot-assisted task-oriented upper extremity skill training in cervical spinal cord injury: a feasibility study. Spinal Cord. 53(7):547-551.

44. Park, W., Jeong, W., Kwon, G.H., Kim, Y.H., & Kim, L. (2013). A rehabilitation device to improve the hand grasp function of stroke patients using a patient-driven approach. IEEE Int Conf Rehabil Robot. 2013:6650482.
45. Jardón, A., Gil, Á.M., de la Peña, A.I., Monje, C.A., & Balaguer, C. (2011). Usability assessment of ASIBOT: a portable robot to aid patients with spinal cord injury. Disabil Rehabil Assist Technol. 6(4):320-330.
46. McCabe, J.P., Dohring, M.E., Marsolais, E.B., Rogers, J., Burdsall, R., Roenigk, K., et al. (2008). Feasibility of combining gait robot and multichannel functional electrical stimulation with intramuscular electrodes. J Rehabil Res Dev. 45(7):997-1006.
47. Bovolenta, F., Sale, P., Dall'Armi, V., Clerici, P., & Franceschini, M. (2011). Robot-aided therapy for upper limbs in patients with stroke-related lesions. Brief report of a clinical experience. J Neuroeng Rehabil. 8:18.
48. Treger, I., Faran, S., & Ring, H. (2008). Robot-assisted therapy for neuromuscular training of sub-acute stroke patients. A feasibility study. Eur J Phys Rehabil Med. 44(4):431-435.
49. Masiero, S., Celia, A., Rosati, G., & Armani, M. (2007). Robotic-assisted rehabilitation of the upper limb after acute stroke. Arch Phys Med Rehabil. 88(2):142-149.
50. Burgar, C.G., Lum, P.S., Shor, P.C., & Machiel Van der Loos, H.F. (2000). Development of robots for rehabilitation therapy: the Palo Alto VA/Stanford experience. Journal of Rehabilitation Research & Development, 37(6), 663-673.
51. Hidler, J., Nichols, D., Pelliccio, M., & Brady, K. (2005). Advances in the understanding and treatment of stroke impairment using robotic devices. Topics in Stroke Rehabilitation, 12(2), 22–35.
52. Datteri, E. (2013). Predicting the long-term effects of human-robot interaction: a reflection on responsibility in medical robotics. Science and Engineering Ethics 19(1), 139-160.
53. Asimov, I. (1951). I, Robot. New York, NY: Gnome Press.
54. Siciliano, B. (2008). Handbook of Robotics. Oussama Khatib: Springer.
55. Sawyer, R.J. (2007). Robot Ethics. Science, 318(5853), 1037.
56. International Organization for Standardization (2014). Robots and robotic devices - Safety requirements for personal care robots. ISO 13482:2014.
57. International Organization for Standardization (2000). Medical devices - Application of risk management to medical devices. ISO 14971:2000
58. Datteri, E., & Tamburrini, G. (2009). Ethical reflections on health care robotics. In Capurro R. & Nagenborg M. (Eds.), Ethics and Robotics (pp. 35–48). Amsterdam-Heidelberg: IOS Press/AKA.

59. Regnaux, J.P., Saremi, K., Marehbian, J., Bussel, B., & Dobkin, B.H. (2008). An accelerometry-based comparison of 2 robotic assistive devices for treadmill training of gait. Neurorehabilitation & Neural Repair, 22(4), 348-354.
60. Hidler, J.M., & Wall, A.E. (2005). Alterations in muscle activation patterns during robotic-assisted walking. Clinical Biomechanics (Bristol, Avon), 20(2), 184-193.
61. Delussu, A.S., Morone, G., Iosa, M., Bragoni, M., Traballesi, M., & Paolucci, S. (2014). Physiological responses and energy cost of walking on the Gait Trainer with and without body weight support in subacute stroke patients. Journal of Neuroengineering & Rehabilitation, 11:54.
62. Dobkin, B.H. (2009). Progressive Staging of Pilot Studies to Improve Phase III Trials for Motor Interventions. Neurorehabilitation & Neural Repair, 23(3), 197-206.
63. Morone, G., Masiero, S., Werner, C., Paolucci, S. (2014). Advances in neuromotor stroke rehabilitation. Biomed Res Int. 2014:236043.
64. Hocoma. Lokomat® User Script. http://knowledge.hocoma.com/fileadmin/user_upload/training_material/lokomat/Lokomat_User_Script_EN_150511.pdf
65. Keller, U., Schölch, S., Albisser, U., Rudhe, C., Curt, A., Riener, R., & Klamroth-Marganska, V. (2015). Robot-assisted arm assessments in spinal cord injured patients: a consideration of concept study. PLoS One 10(5):e0126948.
66. Otaka, E., Otaka, Y., Kasuga, S., Nishimoto, A., Yamazaki, K., Kawakami, M., et al. (2015). Clinical usefulness and validity of robotic measures of reaching movement in hemiparetic stroke patients. J Neuroeng Rehabil. 12:66.
67. Ingemanson, M.L., Rowe, J.B., Chan, V., Wolbrecht, E.T., Cramer, S.C., & Reinkensmeyer, D.J. (2015). Use of a robotic device to measure age-related decline in finger proprioception. Exp Brain Res. Sep 16. [Epub ahead of print]
68. Cappello, L., Elangovan, N., Contu, S., Khosravani, S., Konczak, J., & Masia, L. (2015). Robot-aided assessment of wrist proprioception. Front Hum Neurosci. 9:198.
69. Domingo, A., Lam, T. (2014). Reliability and validity of using the Lokomat to assess lower limb joint position sense in people with incomplete spinal cord injury. J Neuroeng Rehabil. 11:167.

Table and figure legends

Table 1. *Ideal features of a neurorobot*

Table 2. *Clinical trial phases in drug commercialization and motor rehabilitation*.

Figure 1. *The ideal patient -therapist-robot loop.*