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THE ROLE OF ACTION OBSERVATION IN THE RECOVERY AND ACQUISITION OF MOTOR ABILITIES

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Index

Abstract (English)

Via mirror mechanism, action observation can promote neuroplasticity processes underlying motor learning. Following this principle, approaches based on the reiterated observation of an action, followed by its executional attempt, (i.e. action observation training - AOT) are widely adopted for the empowerment of motor skills.

In the **introduction,** the role of AOT for improving existing motor competencies, as well as for the recovery of impaired motor abilities is reviewed and discussed in the light of the neurophysiological framework of human mirror mechanism.

Chapter 1 presents a study aimed at identifying the neurophysiological predictors of motor improvement induced by AOT. For this purpose, transcranial magnetic stimulation (TMS) was used to assess the effects of action observation on corticomotor parameters of 40 healthy subjects. Subsequently, they were administered either an AOT or, as a control, a motor training without action observation. Subjects undergoing AOT showed a higher improvement, which magnitude was associated with the modulations induced by action observation on corticospinal excitability and, even more, on intra-cortical inhibition. Such indexes did not predict controls' improvement, supporting their specificity for the cortical mechanisms underlying AOT.

Chapter 2 explores the peer-to-peer potentiality of AOT, presenting a study evaluating the efficacy of an AOT domiciliary platform promoting child-to-child interaction for hand motor improvement in children with unilateral cerebral palsy (UCP). Here, 20 children with UCP underwent 20 sessions where they had to observe and then imitate a wizard performing dexterity-demanding magic tricks; a child-to-child live video-session to practice the same exercise then took place. Child-to-child based AOT improved hand motor function in UCP, especially in bimanual skills. The improvement was linked to differences in hand motor ability among peers, indicating that children should observe others with superior motor skills to their own.

Chapter 3 reports an experiment evaluating self-body representation in children with UCP enrolled in the study presented in chapter 3. Here, self-portraits are compared to the way children with UCP portray both healthy and hemiparetic peers. The asymmetry index, consisting of the relative difference between the upper limbs length, resulted greater in UCP children's self-portraits in comparison to healthy control's ones. More interestingly, children with UCP portrayed themselves more asymmetrically relative to their classmates and hemiparetic peers, evidencing that UCP affects body self-representation, but not body-representation in general.

Chapter 4 offer a perspective on AOT as an ideal framework for telerehabilitation, discussing the advantages provided by modern technologies (e.g. immersive virtual reality, kinematic sensors) for optimizing treatment delivery.

In conclusion, this thesis presents AOT advances for the recovery and acquisition of motor skills. The novelty of this work is twofold: first, the identification of electrophysiological signatures explaining AOT efficacy may shed light on its underlying cortical mechanisms, envisioning the development of predictive assessments for the selection and identification of best candidates for AOT. Second, by including peer-to-peer interaction, “traditional” AOT may be extended toward novel socially enriched scenarios, where trainees — possibly exploiting digital communication technologies — might simultaneously be recipients and leaders within motor learning process.

Abstract (Italiano)

Attraverso il *meccanismo mirror*, l'osservazione delle azioni promuove i processi di neuroplastictà su cui si fonda l'apprendimento motorio. Partendo da questo principio, il training basato sull'osservazione delle azioni (AOT) è stato adottato per il potenziamento delle abilità motorie.

Nell'**introduzione** sarà discusso il ruolo dell'AOT nell'acquisizione di nuove abilità motorie e nel recupero funzionale in diversi contesti neurologici. Tali applicazioni verranno discusse alla luce del contesto neurofisiologico del *meccanismo mirror* nell'uomo.

Il **capitolo 1** presenta uno studio finalizzato all'identificazione dei predittori neurofisiologici dell'efficacia dell'AOT. Per tale scopo, la stimolazione magnetica transcranica (TMS) è stata utilizzata per indagare l'effetto dell'osservazione delle azioni sull'eccitabilità corticomotoria di 40 soggetti. Successivamente, è stata somministrata ai partecipanti una sessione di AOT, o alternativamente, di training motorio privo di osservazione delle azioni. I soggetti sottoposti ad AOT hanno mostrato un maggior grado di apprendimento motorio, quest'ultimo correlato alla modulazione indotta dall'osservazione delle azioni sull'eccitabilità corticospinale, e, in misura maggiore, sull'inibizione intracorticale. Tali indici, non predicendo l'*outcome* del gruppo di controllo, risultano specifici per i meccanismi alla base dell'efficacia dell'AOT.

Il **capitolo 2** esplora le potenzialità dell'interazione diadica nell'ambito dell'AOT, presentando uno studio che ha valutato l'efficacia di una piattaforma basata sull'interazione *child-to-child* per il miglioramento delle funzioni motorie dell'arto superiore nei bambini con paralisi cerebrale unilaterale (UCP). Venti bambini con UCP sono stati sottoposti a 20 sessioni di AOT in cui veniva loro richiesto di osservare, per poi imitare, un prestigiatore che realizzava giochi di prestigio di fine manualità; successivamente, veniva condotta una sessione dal vivo *child-to-child* finalizzata alla pratica interattiva dell'esercizio appena proposto. Tale approccio si è dimostrato efficace nel miglioramento la funzionalità motoria degli arti superiori, in particolare nelle abilità bimanuali. Il miglioramento è correlato alla differenza di abilità manuali rispetto al compagno di esercizi, indicando che ai fini di un miglior risultato sia preferibile osservare dei soggetti con abilità manuali superiori rispetto alle proprie.

Il **capitolo 3** presenta un lavoro che ha coinvolto una sottopopolazione di bambini reclutati nello studio precedente, in cui è stata valutata l'autorappresentazione corporea mediante autoritratto, confrontando quest'ultima con la rappresentazione dei propri pari, emiparetici o sani. L'asimmetria di rappresentazione degli arti superiori è risultata superiore negli autoritratti dei bambini con UCP rispetto a quelli di una popolazione di

controllo. Inoltre, i bambini con UCP hanno ritratto sé stessi più asimmetricamente rispetto ai loro pari, evidenziando che tale condizione clinica influenza l'auto-rappresentazione corporea, ma non la rappresentazione corporea in generale.

Nel capitolo 4 è stato prospettato l'utilizzo dell'AOT come approccio elettivo nell'ambito della teleriabilitazione, discutendo i vantaggi apportate dalle più recenti tecnologie per l'ottimizzazione della somministrazione dell'AOT.

La tesi presenta un duplice aspetto di originalità. Il primo consiste nell'identificazione di marcatori elettrofisiologici che predicono l'efficacia dell'AOT, attraverso cui sarà possibile elucidare i suoi substrati neurofisiologici, favorendo lo sviluppo di modelli predittivi per l'identificazione dei candidati ideali. Il secondo risiede nell'introduzione dell'interazione diadica, grazie alla quale l'AOT "tradizionale" potrà essere estesa a scenari sociali, in cui i destinatari del trattamento saranno al contempo "beneficiari" ed "erogatori" all'interno del processo di riabilitazione.

Introduction

The role of mirror mechanism in the recovery and acquisition of motor abilities.

This chapter is based on the article: *"The role of mirror mechanism in the recovery, maintenance, and acquisition of motor abilities"*, by Rizzolatti G., Fabbri-Destro M., Nuara A., Gatti R., Avanzini P. Neuroscience & Biobehavioral Reviews, Volume 127, 2021, Pages 404-423.

Action observation is incorporated into several daily routines to improve our motor skills. We learn complex movements by observing and imitating models; we sharpen our motor skills by reiteratively observing and analyzing our previous performance; we use action observation to adjust our performance in the case of decaying or suddenly impaired motor skills. Although these applications predate the discovery of the mirror neurons, the human mirror mechanism represents the ideal neurophysiological background to connect all the dots in a single neurophysiological and theoretical framework. Such a unitary view would help identify the neural mechanisms common to diverse applications. At the same time, it could guide the refinement of existing applications and the development of new ones based on neurophysiological grounds. To this aim, here is presented a narrative review connecting AOT applications, spanning from the rehabilitative field to motor learning.

1. Neural bases of the Action Observation Treatment

Typically, we start voluntary movements by activating higher-order cortical motor areas located in the frontal lobe and the cingulate cortex. However, the execution of a voluntary movement is facilitated when the to-be-initiated action corresponds with an observed action executed by another individual [1, 2]. This congruence between action observation and execution has been called *ideomotor mechanism* by Greenwald [3] and is considered the basis of imitation. Although it has been debated whether ideomotor compatibility or association processes underlie imitation [4], the work by Prinz and coworkers [5, 6] provided convincing evidence that the ideomotor compatibility represents the fundamental schema transforming observed actions into their execution. According to such a mechanism, "*perception of another person's action […] can trigger the same action in the observer because perceptual event representations and representations of actions share a common representational domain*" [7].

Neurophysiological findings obtained in the last twenty years have demonstrated that imitation is based on a mechanism similar to that postulated by Prinz. However, while

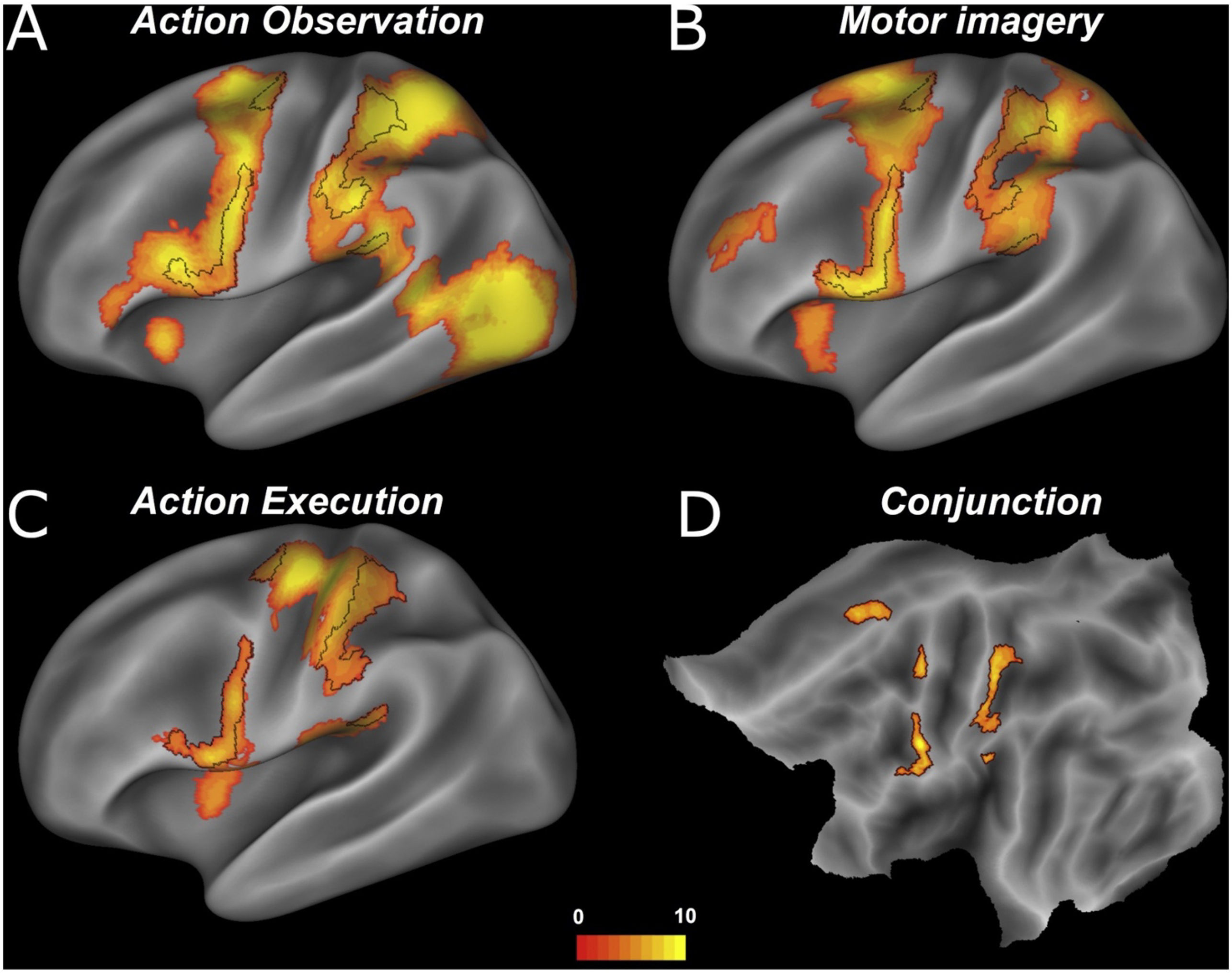
Prinz postulated the presence of an amodal center - neither motor nor sensory - mediating the imitative process, later neurophysiological data showed that imitation relies on a direct transformation of sensory information into motor activity [8].

This direct transformation has been initially discovered in the premotor cortex [9]. Indeed, in this area are present neurons discharging both during action execution and in response to sensory information representing the same action. These neurons have been called *mirror neurons*. A series of subsequent studies in monkeys and humans demonstrated that a general mechanism transforming different types of sensory information into a motor representation is present in several cortical areas, including the posterior parietal cortex [10], the insula [11] and the cingulate cortex [12, 13]. This mechanism was called the *mirror mechanism*. The initial studies reported that the mirror mechanism was activated by the observation of simple goal-directed actions, like grasping, pushing, dragging, or braking [14, 15]. Subsequent investigations showed that also the observation of more complex actions, like climbing [16], hand manipulation [17], or tool use [12, 18] activates a pattern of motor areas coherent with action execution.

Neurophysiological evidence of *direct imitation* in humans was first provided by Iacoboni and coworkers [8] in a functional magnetic resonance imaging (fMRI) experiment. Participants were asked to observe and imitate a finger movement and perform the same movement following a spatial or symbolic cue presentation. The results showed that the opercular region of the left inferior frontal cortex and the rostral-most part of the right superior parietal lobule - two areas with mirror properties - were more strongly activated by the observation of finger movements identical to those asked to be imitated, rather than by the observation of different finger movements or symbolic cues.

The neural bases of *imitation learning* were addressed by Buccino et al. [19], also using fMRI. Naive participants were scanned during four phases: 1. observation of guitar chords played by a guitarist (action observation); 2. a pause following observation during which the participants were instructed to perform motor imagery of the observed actions (motor imagery); 3. active performance of the observed chords (execution); and finally 4. rest. The results indicated that the inferior parietal lobule and the inferior frontal gyrus (i.e., mirror network) keep active during the whole imitation learning process, i.e., throughout action observation, motor imagery, and execution. This fronto-parietal network started to be active since the observation of the guitar chords, persisted during the following motor imagery with the additional recruitment of the middle frontal gyrus (area 46), and remained active also during the chords execution, together with motor and somatosensory areas. In a recent meta-analysis, Hardwick and colleagues [20] investigated the respective networks underlying the three stages (action observation, motor imagery, and action execution) over hundreds of neuroimaging experiments, providing a comprehensive map of the neural substrates of each phase (Figure 1, panel A-C). Further, the three maps' conjunction renders a reliable picture of the fronto-parietal regions endowed with the mirror mechanism (Figure 1, panel D).

Fig. 1. Neural substrates of action observation (AO, panel A), motor imagery (MI, panel B), action execution (AE, panel C), and conjunction across AO, MI, and AE (panel D). Adapted from Hardwick et al., 2018.



The schema of the experiment by Buccino [19] - observation, motor imagery, and execution - represents the scaffold of the Action Observation Treatment (AOT). This treatment, used in motor rehabilitation and motor training, starts with the observation of actions to be performed. Action observation has been proven to induce, even in isolation, lasting changes in excitability within M1 cortical representations of muscles/movements involved in observed and executed actions in healthy individuals [21] and stroke patients [22]. Of note, functional reorganization of the primary motor cortex is a crucial index of neuroplasticity, associated with functional improvement and motor skills empowerment [23–26].

The main effect of AOT onto the cortical motor system is the potentiation of the proper motor program (i.e., the series of cortical and subcortical activations leading to the execution of a given action) across premotor and parietal sites. How does this potentiation impact the motor execution? Different anatomical substrates might underlie the motor improvement driven by AOT. One possibility is that premotor activation increases the excitability of M1; an alternative possibility is that the direct projections descending from premotor regions determine the behavioral improvement [9]. There is also evidence in the monkey that action observation might directly activate M1 neurons giving origin to corticospinal pathways [27].

Although action observation *per se* could lead to positive outcomes, there is evidence that linking action observation with action execution *via* motor imagery, i.e., asking subjects to rehearse the action previously observed, sets the premises for an optimal outcome. Motor imagery was extensively studied by Jeannerod, who defined it as "an internal motor representation lacking only of the final execution of the action" [28]. Because able to activate the primary motor cortex [29], motor imagery can be regarded as an "intermediate step" in the gradient of motor activation going from action observation to action execution. Evidence demonstrating activation of the motor cortex during motor imagery derives from TMS experiments [29] indicating a decrease of motor cortex threshold for achieving overt movements and from EEG studies [30] showing a desynchronization of EEG-rhythms somatotopically organized in the correspondence of the precentral gyrus. Motor imagery as such has been proposed as a motor rehabilitation procedure. However, heterogeneous results in terms of effectiveness have been found [31]. Furthermore, this technique became challenging to perform with continuity by patients and to be monitored by experimenters and clinicians [32].

Chaining together action observation, motor imagery, and action execution in a sequential procedure would, in turn, merge reciprocal advantages. Indeed, while action observation is already capable of activating the fronto-parietal network underlying a given action, successive motor imagery prolongs this activation in time, extending the recruitment to a wider cortical network. The final motor execution would then be facilitated by the progressive pre-activation of its neural substrates due to the two previous stages.

Thanks to its capacity to activate the motor system regardless of the movement capacities of the beneficiary, AOT represents a valuable tool to intervene on the motor system and positively bias the trajectory of the motor skills during motor recovery or motor training.

2. AOT and motor skills acquisition

2.1 Training in sports

For many years now, sport theorists and trainers have discussed the utility of using cognitive training in addition to active-motor training. Initially, they were primarily concerned with the use of motor imagery of the action to be performed. Subsequently, training procedures based on motor imagery were complemented or even substituted with those based on AOT, which became popular among practitioners and trainers.

Two are the main effects induced by using AOT in sports training: a) the improvement of the motor skills of the athletes; and b) the improvement of their capacity to predict the intention of the opponent in order to respond more appropriately to his/her moves. The neural bases for performance improvement are very similar to those necessary for rehabilitation in clinical conditions. Needless to say, intensive specific practice for a given sport is a first pre-requisite for becoming an elite athlete. To start practice early is essential for a future elite athlete.

An essential difference between elite athletes and novices is represented by the increasing automaticity in the first category without the necessity of controlled processes demanding attention. These automatic processes are rapid, smooth, effortless, and demand little attentional capacities [33]. Recent studies in the development of expertise showed that most young athletes fail to develop beyond a hobbyist level of performance precisely because they settle into automaticity at a skill level that they find enjoyable instead of continuing to improve [34].

It is well established that complex behavior learning (e.g., swinging a golf club) requires the acquisition of coordination of muscle forces. In an experimental study, Mattar and Gribble [35] provided evidence that mechanisms matching observation and action facilitate motor learning. Participants observed another person performing an action, either with increasingly better performance (learning) or random performance (no learning). When later required to execute the observed movements, participants of the first group had better performance than those of the second group. These findings demonstrated that watching another individual learning a task has an adjunct value relative to action observation only.

Similar results were obtained in a series of studies that evaluated the benefits of observational motor learning during sports skills acquisition. Boschker and Bakker [36] examined whether observing an expert climber would enable inexperienced climbers to acquire new strategies for their action, improving their climbing performance. The results showed that after model observation, the inexperienced climber performance was biased towards the observed strategy, proving that observation per se can prime the motor system for upcoming action.

Whether visual demonstrations or verbal instructions are more effective instructional constraints for the acquisition of movement coordination was investigated in dart-throwing practitioners. The kinematic analysis revealed that compared with verbal instructions or no instructions, visual demonstrations significantly improved participants' approximation of the model's coordination pattern [37].

Similar findings were obtained by Breslin and coworkers [38] in cricket. Videos or point-light displays of cricket bowlers improved the kinematic performance of trainees, while single dots placed on the wrist reproducing end-effector trajectory did not exert the same effect.

The quality and rate of change in intra-limb coordination were evaluated by Horn et al.[39] in baseball novices throwing a ball towards a target with maximal velocity using a back-handed, reverse baseball pitch following two training procedures. In the first, participants observed a video model; in the other, they practiced using verbal guidance only. Interestingly, the video model group, but not the verbal guidance group, changed their intra-limb relative motion imitating those of the model. This new coordination pattern was maintained throughout the acquisition without further change.

In addition to the data demonstrating an improvement of motor abilities by observing actions made by others, there is evidence that the observation of actions in experts in specific performances determines a stronger activation of the neural substrate underlying the execution of those actions, relative to naïve individuals. Calvo-Merino and coworkers[40] investigated in an fMRI experiment the mirror responses of three different groups of participants: classical dancers, dancers of Capoeira, and people naive to dancing. Stimuli consisted of videos of either Capoeira or classical dance steps. A double dissociation was found between the two expert groups. Mirror responses to Capoeira steps were stronger in the Capoeira experts, and vice-versa mirror responses to classical dance steps were stronger in ballet experts.

In a further experiment, the same researchers [41] disentangled whether the mirror response is mostly driven by the visual familiarity of the observers with dance steps or by their motor expertise. They studied classical ballet and examined in men and women the activation determined by observing steps done by dancers of the same or different gender. They found that frontal and parietal areas were more strongly activated by observing steps executed by individuals of the same gender as the observer. This finding indicates that motor expertise - and not visual experience - is crucial in modulating the mirror mechanism.

The data by Calvo-Merino were extended by Cross and coworkers [41]. In their study, expert dancers observed and rehearsed-to-learn novel complex whole-body dance sequences across five weeks. Brain activity was recorded weekly by fMRI while dancers observed and imagined themselves performing different movement sequences. Half these sequences were rehearsed, and half were unpracticed control movements. After each trial, participants rated how well they could perform the movement. Dancers' ratings of their ability to perform rehearsed sequences, but not the control sequences, increased with training.

When dancers observed and rehearsed another dancer's movements, brain regions classically associated with motor imagery and action observation were active. Critically, inferior parietal lobule and ventral premotor activities were modulated as a function of dancers' ratings of their ability to perform the observed movements and their motor experience. Therefore, the authors suggested that a complex motor behavior can be learned de novo over five weeks of rehearsal and that the enhancement of activity in premotor and parietal areas is irrespective of stimulus familiarity.

Concerning the capacity to predict the intention of an opponent or a teammate, there is evidence that experts are superior to less skilled players in detecting a series of cues which allows them to anticipate the moves of opponents, the opponent action preferences, and most importantly, the meaning of opponent's body posture [42, 43]. In other words, it is fundamental for the observer to understand the intention of the opponent before his/her action starts in order to have an appropriate and prompt response.

Note that often two different concepts are pooled together under the term "intention prediction". The first is the prediction of the agent action outcome, the other of what the agent will do subsequently (i.e., the upcoming motor act). Examples of outcome prediction may be taken from studies of tennis, basketball, baseball, rugby, badminton (see Bishop et al. [44]), most of them using temporal occlusion paradigms. This type of paradigm consists of presenting a dynamic stimulus interrupted at different delays from its onset. Domain-specific motor experts and novice participants are required to predict the outcome of the movements after viewing only the initial body kinematics of the performer or the visual consequences of the movements (e.g., ball trajectory). Research in various sports showed that motor experts are more accurate than expert observers (like fans, sports journalists, and coaches) and novices in predicting the outcome of the observed actions after viewing the initial body movements [45, 46].

A paradigmatic situation is the tennis serve. In a study by Abernethy and Russel[47], participants viewed video clips of an opponent performing tennis serve; these clips were foreshortened at various points relative to racketball contact to provide different degrees of information. Experts consistently detect kinematic information at very early, pre-contact levels of occlusion to successfully determine the direction of the ball and the force with which it is struck [48, 47, 45].

Both motor and visual familiarity (i.e., expert athletes and expert observers) may lead to earlier and more accurate predictions of the outcome of an action. However, while expert observers base their predictions on visual cues like the initial ball trajectory, elite athletes rely more on visuomotor cues like the body kinematics and postures of the opponents [49–52].

The second aspect of action prediction is reading in advance what will be the opponent's next move. In fact, in team sports, players often aim to deceive or mislead others, attempting to limit available information or provide misleading cues that make the observers more error-prone [53]. Fooling behaviours can be divided into attempts to mask the player's genuine intention or provide information that leads the observer to make an incorrect prediction. Studies of movement kinematics during fooling actions in sports [54, 55] have shown that players try to reduce the kinematics information that is crucial for performing the intended action (e.g., the orientation of the feet during a soccer penalty kick) and to emphasize those less relevant for action performance (e.g., shaking of the upper limbs of the kickers).

Studies on rugby [53], basketball [56], and handball [57, 58] have shown that expert players are better than novices at recognizing when other players are attempting to deceive them. In particular, by using a temporal occlusion paradigm, Jackson et al.[53] showed that expert players could recognize the opponent's deceptive intentions by merely observing their initial body movements.

The neural substrates underlying the capacity to predict others' actions have been investigated by neurophysiological studies showing the relationship between motor intention and mirror activity. The first study providing evidence for this was conducted in monkeys in a single-neuron recording study. The experiment consisted of two parts [10]: In the first part, monkeys were trained to grasp an object with two different intentions: eating it or placing it in a container (motor paradigm). In the second part, monkeys observed the experimenter grasping the same object with the same intentions (visual paradigm). Neurons were recorded from the inferior parietal lobule (IPL), and their discharge during grasping was studied in the motor and visual paradigm. The results obtained during active movements showed that many IPL grasping-neurons discharge with markedly different intensity according to the intention of the action (i.e., eating or placing).

The second part of the experiment (visual paradigm) aimed to determine whether the visual responses of grasping neurons were modulated by the intention of the actions in which grasping was embedded. The observed agent's intention modulated most of the IPL mirror neurons' discharge, thus showing that the observation of the action and context allows one to understand the agent's intention. Similar results were subsequently found in the premotor areas (F5) of the monkey [59].

The existence in humans of a similar organization during the performance of intentional action and the understanding of the observed agent's intention was demonstrated by Cattaneo et al. [60] using electromyographic recordings in children and by Iacoboni et al. [61] using functional magnetic resonance in adults.

2.2 Training in music

Musicians' repertoire arises throughout a lifelong practice involving perceptual, motor, and cognitive domains and is sustained by efficient coupling of musical stimuli with their correspondent motor representation [62, 63]. The importance of the close relationship between music perception and production is underlined by several pedagogical approaches based on the reiterate evocation of motor representations through visual and auditory music-related stimuli. For instance, some masters suggest pupils listen back to just practiced music to improve their instrumental performance [64]. Other times - especially in the first years of training – pupils are requested to observe, rehearse, and then imitate the master’s hand movements to shape a proper manual postural attitude [65–67]. The imitative motor scaffold of music learning is even more emphasized in ancient music. For example, in *Karnatic* and *Hindustani* musical systems, music is mostly orally transmitted from master to pupils [68], and in Suzuki’s pedagogical method, the preliminary learning stage is indicated as *minarai kikan* (i.e., literally *“period of learning by watching”)*[69, 70].

Given this framework, a brain mechanism able to directly transform a music stimulus into a related motor representation could be exploited in the realm of music training. Pivotal neurophysiological experiments on monkeys demonstrated that ventral-premotor neurons might discharge not only during the execution of a specific action but also when the same action is just “heard” [71, 72]. Of note, most of these neurons (75%) were also visually selective for the same action, suggesting that both auditory and visual inputs converge in a motor representation within the motor system. Such “audiovisual” mirror neurons, accessing to the own motor vocabulary of action schemas and goals, can be recruited to recognize others’ actions - even if only heard – through the evocation of the corresponding motor programs [71]. The convergence of listening and observation of actions on a common motor representation gives an “extra weapon” to contribute to music training by exposing trainees to music-related stimuli.

Parallel to the hierarchy of action organization in which several motor acts are chained to form action with a specific goal, music can be seen as the process of chaining together several single notes to form a melodic sequence. A crucial question, then, would be whether such an audio-motor matching mechanism preferably involves the single notes or the whole melodic sequence. Lahav et al. [73] addressed this issue, first training non-musicians to play a specific melodic sequence and next studying their fMRI brain activity while listening to either the recently acquired or new musical sequences formed by the same notes. Trained melodies evoked bilateral brain activation in the fronto-parietal network, particularly within the left IFG, while new melodies activated the same network, but to a lesser degree. In a further control condition, previously listened – but not practiced - melodies were used as stimuli, but this did not elicit any fronto-parietal activation. Overall, these findings support the existence of a mechanism matching hearing and doing in the listener's motor system, likely mainly encoding the action generating the whole melody rather than the single notes, consistently with the acquired motor repertoire.

Haueisen and Knösche [74] provided one of the earliest indirect evidence of mirror mechanism in advanced music expertise, studying pianist and other musicians' brain activity while listening to piano pieces belonging to pianist's repertoire. Magnetoencephalographic (MEG) data highlighted - only in pianists - an increased activation in the motor cortex contralateral to the hand associated with the execution of listened notes, with a topographical specificity of correspondent fingers' motor maps.

A subsequent series of fMRI experiments [75–77] investigated brain networks subserving the coupling between musical action and its perception in professional musicians, comparing the brain activity occurring during silent-piano execution to that related to mere listening to corresponding piano sounds. Only professional musicians showed overlap between areas recruited during music listening and execution, including supplementary motor and premotor areas, dorsolateral and inferior frontal cortex, and supramarginal gyrus. Noteworthy, the topographic distribution of such activation was similar to that described in other studies on the observation of musical gestures in musicians [65], suggesting that a common mechanism may be able to mirror both visual and auditory stimuli into a common motor representation of music-related gestures.

Even if capable of detailing the topography of the networks shared by music listening and production, fMRI does not allow to study changes in motor cortex excitability. This aspect has been investigated in a Transcranial Magnetic Stimulation (TMS) study, where the modulation of cortico-spinal excitability evoked by listening to practiced music was assessed in piano players before and after a training [78]. Here, the authors found a gain of

MEP amplitudes at the end of the training period, indicating that listening to acquired music instantiates a cortico-spinal motor facilitation.

Other electrophysiological evidence showing that listening to practiced melodic sequences induces motor facilitation has been recently provided by EEG studies describing an increase of motor activity – in terms of suppression of mu-rhythm - associated with the mere listening of melodies belonging to the own repertoire of the listener [79].

In addition to the listening-to-play approach, even the observation of musical actions may play a key role in music training. Haslinger et al. [65] explored the neuroimaging correlates of multimodal sensorimotor transformations in musicians during the perception of different, modality-specific, music-related stimuli. While observing pantomimed piano-playing actions, pianists showed higher activations in fronto-parietal networks compared to music-naïve subjects. The observation of mute piano playing was able to extend the recruitment to auditory regions in pianists; finally, listening to piano sounds coupled with hand movements evoked increased activation to a greater extent within sensorimotor networks, including the posterior part of the inferior frontal gyrus, the ventral part of the lateral premotor cortex, the inferior parietal/intraparietal cortex and the temporal cortex within the STS.

These findings indicate that the simultaneous delivery of multimodal stimuli related to the same action can activate sensorimotor networks to a greater extent than the unimodal approach. A pre-existing sensorimotor repertoire coherent with the perceived stimuli enhances such a "mirror" activation.

Thus, as musicians' repertoire enriches over time, the consistent administration of visual and auditory stimuli concerning the to-be-trained music would enable them to "internally" play - thus practice - the perceived melodies, even without moving hands. Such an approach, grounded on the multimodal exploitation of the mirror mechanism, might constitute the neurophysiological basis of various teaching methods adopted in musical cultures worldwide and the ground for complementary training procedures in music.

2.3 Training in surgery

Beyond promoting the improvement of patients' motor abilities, observational learning can bring substantial benefits to the "provider" side of healthcare, especially in improving motor abilities in disciplines requiring fine motor control in daily procedures.

Surgery represents a paradigmatic example, as perfectioning of surgical motor abilities is of utmost importance. Among surgical skills, hand dexterity represents one of the most significant, as the accuracy and speed of fine-hand movements are major determinants of a successful surgical task [80]. It is widely accepted that, before exposure to surgical interventions, the formal demonstration of procedures and the observation of surgeries in the setting of operating theatre are the main elements of early surgical training.

However, attending the operating room is not always possible, and the current need to optimize patient care and reduce waiting times may strive with the need for delivery of surgical training. Observational learning might represent a promising approach for sustaining surgical skill acquisition in parallel to experience in vivo [80].

The effectiveness of observational learning in surgical practice was first demonstrated in a study by Custers et al. [81], where students who watched videotapes in which expert surgeons demonstrated a specific surgical task performed better than subjects who did not watch any model, both in terms of the quality of the surgery and speed. Subsequent studies confirmed the goodness of expert model observation for surgical practice, adopting more advanced technologies, such as VR-based simulators [82].

However, a large body of studies suggests that - besides the observation of expert actors - also viewing errors made by imperfect models may favor the development of the error detection and correction abilities, ultimately improving motor skills [83, 35, 84]. In the field of surgery, the effect of "error observation" was first investigated by LeBel et al. [85] in a randomized study where participants had to observe either an expert surgeon or an untrained novice performing a simple arthroscopic localization task. Interestingly, both groups improved to a comparable extent in the majority of endpoints, but at a one-week follow-up, the novice-observation group showed a higher improvement in comparison to the expert-observing one. This indicates that observing both expert and "imperfect" models favor the complex motor procedures' learning, possibly relying on different, but complementary mechanisms: while the observation of experts may evoke – and thus consolidate - the correct motor schema, observing errors may enable processes of error detection and correction (see also Harris et al. [86]).

Based on the above-described findings, it has been pointed out that the delivery of a "mixture of expert and novice models would provide the greatest benefit for learning, through the development of error detection and correction mechanism from the novice, and the ideal blueprint from the expert" [80]. In other words, the traditional master-pupil approach should be flanked by a dyadic learning model in which, observing the mistakes of other trainees, learners would avoid making similar errors.

A final practical benefit of observational learning in surgical training consists in its time- and resource- efficiency due to its deliverability to broad groups of trainees through videos, virtual-reality-based simulators, and online platforms [80]. Indeed, learning by observing experts or peers may constitute a cost-effective way of acquiring and consolidating a considerable variety of surgical skills, enabling trainees to improve their abilities at any time and from any location [80, 87].

3 AOT and motor rehabilitation

3.1 Orthopedics, traumatology, and other peripheral disorders

Traditionally, the rehabilitation of patients with traumatic/orthopedic disease was based on manual therapies, active movements of the affected part of the body, and execution of functional tasks. This approach is justified by the necessity to recovery autonomy, restoring the efficiency of the muscolo-skeletal functions of the impaired body part. More recently, a large number of studies both in animals and humans showed that the modifications induced by traumatological injuries are not limited to the muscolo-skeletal districts but may involve the whole motor system, including its cortical level [88–90]. This aspect should be considered in motor rehabilitation, *combining* AOT interventions with classical rehabilitative strategies.

It is important to note that exercising a specific body part increases the extent of its cortical representation. An impressive demonstration of this effect in humans was shown by the expansion of the neural representation of the working hand in individuals who practice highly specialized sensorimotor activities such as playing the violin or reading Braille [91, 92]. This process of cortical plasticity can be seen as 'positive', as it underlies a motor potentiation. However, active exercising is not always possible, in particular when referred to post-injury conditions. The mirror mechanism represents a viable way to reproduce the neural motor program (i.e., the sequence of neural activities occurring during action execution) even in the impossibility of actual movement[9].

During immobilization or restrained limb use, two phenomena tend to take place at the cortical level. On one side, the motor representation of actions correctly executed with the limb becomes less efficient, being untrained over time [93]; on the other side, movements execution is altered to deal with the deficits, and these compensatory movements tend to establish maladaptive motor programs competing against the normal one. In a dual perspective, such cortical plasticity processes can be seen as 'negative'.

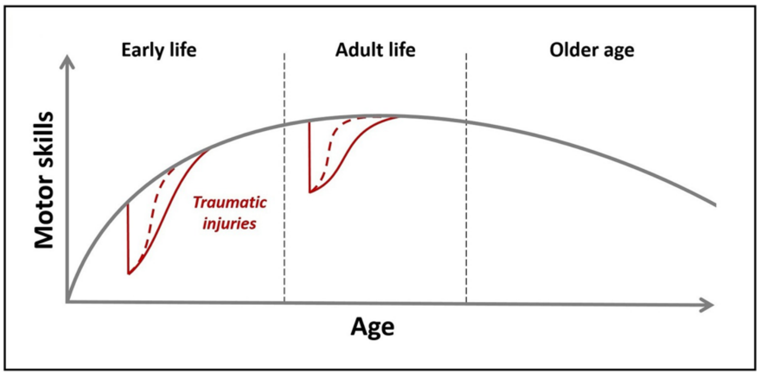
Long-term, chronic effects of negative cortical plasticity have been described by Merzenich [94] and Pons [95], revealing that the deafferentation of the sensory inputs modifies somatotopic maps of the body surface. Although plastic reorganization in the cerebral cortex has been traditionally considered to occur exclusively during development, these studies demonstrated that it may also occur in adulthood and that cortical maps are alterable throughout life.

Subsequent studies documented that the mechanisms of positive and negative plasticity also extend to the motor system. In 1996, Nudo and Milliken [96] showed that a small lesion in the hand area of the adult squirrel monkey results in a further loss of hand territory in the adjacent, undamaged cortex. In a later study [23], the same group documented how the retraining of skilled hand use after similar lesions resulted in preventing the loss of hand territory adjacent to the lesion. Taken together, these pieces of evidence parallel the notions of positive and negative cortical plasticity discussed above.

A series of subsequent studies in humans indicated that physiological or pathological perturbations of somatic input and motor output might induce neuroplastic changes at different somatosensory and motor systems levels [97, 98]. Indeed, remapping processes were proven to follow the reduction of somatosensory input and motor output in amputee humans [88–90] and to occur in patients with short- or long-lasting peripheral deafferentation [99–101]. TMS studies subsequently confirmed these findings. Facchini [102] tested the excitability of the right primary motor cortex (M1) in healthy subjects following the left fourth and fifth fingers immobilization. The results showed a substantial decrease of motor cortical excitability related to the constrained muscle with an extension of the cortical map to adjacent non-constrained finger cortical representation. Comparable results were recently obtained by Bassolino and coworkers [93].

The evidence reviewed above suggests that - in addition to peripheral rehabilitation - it is important to include strategies promoting positive cortical plasticity while counteracting the establishment of maladaptive compensatory motor reorganization. This aspect could turn fundamental for patients with prolonged immobilization and inactivity after peripheral injury or surgery, leading to severe and long-lasting motor dysfunctions. A possible intervention to maintain an active cortical representation of the non-used body part is represented by Action Observation Treatment (see Fig. 2 for a graphical model of motor skills trajectory following traumatological impairment).

Figure 2. AOT effects on motor skills trajectory following traumatological events. The continuous grey line indicates the neurotypical motor trajectory in the absence of any traumatic condition. Solid red lines show how trajectories deviate from the original one in the case of traumatic events. Dashed red lines indicate how the administration of AOT modifies pathological trajectories.



This strategy was first applied to patients recovering after orthopedic surgery by Bellelli and coworkers [103]. The study was conducted on 60 post-orthopedic surgery patients (hip fracture or hip or knee replacement) randomly assigned to either an experimental or control group. Patients in the experimental group were asked to observe video clips showing daily actions and to imitate them afterward. Patients in the control group were asked to observe video clips without motor contents and execute the same actions as patients in the experimental group. The rehabilitation program lasted for three weeks, six days a week, one hour per day. After a baseline evaluation (t0), a functional assessment was repeated once a week for the whole treatment (t1, t2, and t3). Besides the motor evaluation scales, changes in the use of walking aids from admission to discharge and the time to the possibility to use one crutch during post-rehabilitative training were considered as outcomes. At t2, more than half of the patients in the experimental group used one crutch in comparison with approximately 10% of the control group. At t3, all patients except 1 in the experimental group used one crutch, while more than 20% of the controls still used two crutches. The results of this study demonstrate that AOT fastens the recovery of motor impairment in patients after orthopedic surgery for hip fracture or elective hip or knee replacement.

Two studies using AOT were conducted by Villafañe and coworkers [104, 105] with patients after total hip arthroplasty. In the first study, the experimental group observed actions (AOT), while the control group received written information about exercises to be executed. Several outcome measures were collected, including the hip range of motion and self-administered questionnaires about quality of life and daily living activities. While no difference emerged between groups in terms of functional measurements, AOT improved perceived physical function more than written information, making patients more confident in self-perceived health than physical activities commonly performed in daily living. In the second study [105], AOT was contrasted with the observation of natural videos without motor contents. Contrary to the previous study, a between-group difference in terms of functional outcomes emerged, with larger active flexion and extension of the knee in the group of patients treated with action observation treatment. The different pattern of results between the two studies might be related to the differences in the control conditions: while in the first study control patients read written instructions about the exercises, which could elicit motor imagery and thus obscure the difference between the two groups, in the second study control stimuli are devoid of any motor content, thus leading to a larger effect size.

Positive results about the effectiveness of AOT onto functional measures were also confirmed by additional studies, further suggesting beneficial cascade effects. Park and coworkers [106] reported that AOT reduces pain and stiffness in patients undergoing total knee arthroplasty. More recently, Marusic and coworkers [107] demonstrated that two months of additional nonphysical training, including action observation, improved functional and cognitive rehabilitation outcomes in patients with unilateral total hip replacement relative to the standard rehabilitation program alone.

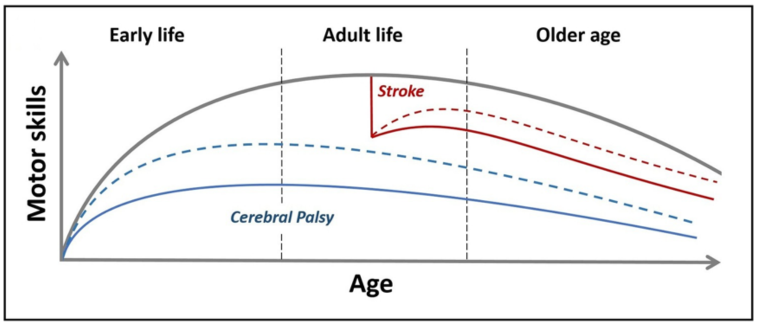
From a neurophysiological perspective, AOT can represent the essential ingredient to limit negative plasticity processes - and at the same time to favor positive ones – in patients whose peripheral damage partially or hinders movement execution. Indeed, the sustained motor activity during action observation and motor imagery may prevent the maladaptive reorganization of motor areas, thus counteracting the progressive motor worsening due to limb motor inactivity [103, 104, 107]. At the same time, AOT could reinforce and consolidate the previous motor program hindered by the prolonged immobilization, thus allowing a faster motor recovery of the impaired function.

Given its physiological background and operational principles, AOT use could also be extended to other disorders of the peripheral nervous system such as traumatic nerve injuries, Guillain-Barré syndrome, and neuromuscular disorders, where the role of AOT in preventing the maladaptive cortical changes [93, 108] would promote more prompt and efficient motor recovery.

3.2 Brain Injury

There is growing evidence that AOT may positively affect the rehabilitation of movement and language deficits following stroke and the treatment of motor deficits in children with cerebral palsy (see Fig. 3 for a graphical model of motor skill trajectory following brain injuries). We will examine these three clinical conditions separately.

Figure 3. AOT effects on motor skills trajectory following brain injuries. Continuous grey line indicates the neurotypical motor trajectory. Solid lines show how trajectories deviate from the original one in the case of brain injuries. Dashed lines indicate how the administration of AOT modifies pathological trajectories.



3.2.1. Motor deficits in stroke

Stroke is a leading cause of neurological disability worldwide. Motor deficits occur in more than 80% of patients [109]. They lead to limitation of patients mobility and, consequently, to a reduced quality of life [110]. Among motor deficits, those concerning the upper limbs represent the most frequent and severe functional impairment following a stroke, occurring in about 77% [111].

Therefore, it is not surprising that AOT was first applied to the rehabilitation of upper limb motor functions. In a pivotal study, Ertelt et al. [112] demonstrated that the observation of daily actions administered for four weeks improves motor functions in chronic stroke patients with upper limb motor deficits. Interestingly, fMRI data acquired during a standardized sensorimotor task before and after treatment showed that AOT increased responsiveness over a mirror network, including the ventral premotor cortex, supplementary motor area, and the supramarginal gyrus.

In a further experiment, Celnik et al. [22] investigated whether AOT induces changes in corticospinal excitability in motor-impaired stroke patients. In a Transcranial Magnetic Stimulation (TMS) experiment, they showed that the observation of a previously trained action was associated with increased excitability within the primary motor cortex of the same muscles congruently involved in the observed action.

After the first explorative investigations, the clinical effectiveness of AOT in improving hand motor function in stroke was tested and confirmed in several observational [113], randomized-controlled [114–131] and within-subjects [132] studies.

An intriguing possibility in rehabilitation consists in associating the observation of task-oriented hand movements with non-invasive brain stimulation techniques (e.g., repetitive Transcranial Magnetic Stimulation - rTMS) to facilitate motor recovery following stroke. A randomized pilot study conducted by Noh et al. [133] in patients suffering from a subacute stroke showed that the administration of inhibitory rTMS over the contralesional hemisphere combined with the observation of actions led to a more remarkable improvement of distal hand motor function in comparison to the rTMS alone. However, the sizeable intra-individual variability in movement execution proper of the subacute population may require caution to interpret these promising findings. A deeper understanding of motor reorganization driven by AOT along subacute and chronic phases of stroke is needed to plan future brain stimulation protocols associated with this technique properly.

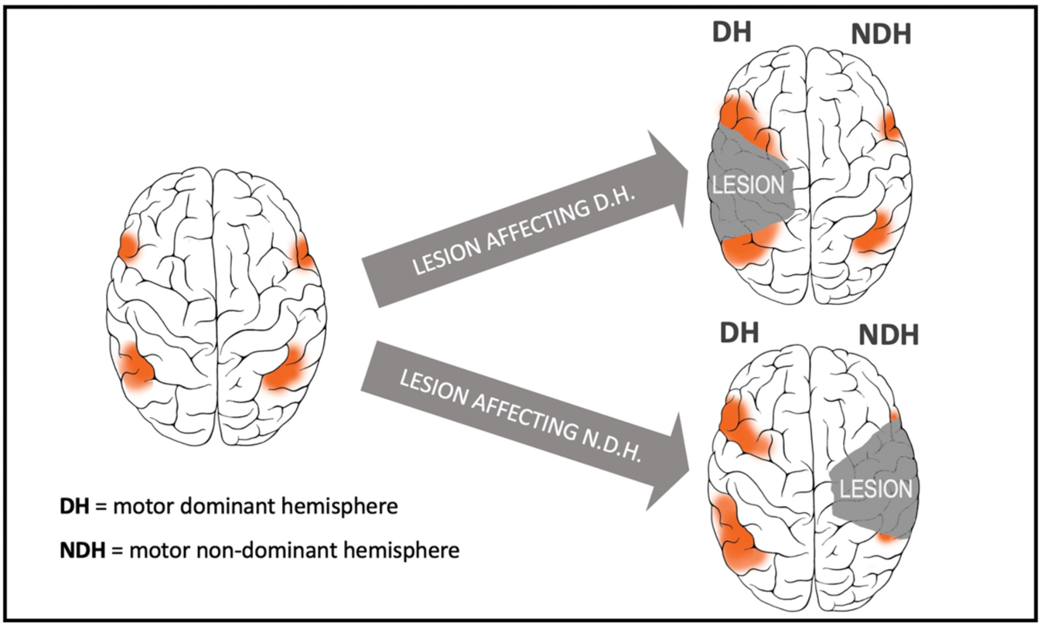
In this regard, Brunner et al. [134] performed a longitudinal fMRI study investigating brain activity during both action observation and action execution immediately following stroke event and at a three-month follow-up. While the activity of sensorimotor areas during action execution was reduced over time, the activation of regions endowed with mirror mechanism during action observation increased and was correlated with the motor improvement. These findings suggested that higher visuomotor responsiveness to action observation might indicate and – possibly – predict the post-stroke improvement of motor function, regardless of the brain fluctuations of the brain activity following damage.

In addition to hand motor impairment, gait and postural deficits are significant determinants of motor disability in stroke. These disturbances affect two out of three stroke survivors [135] and have a detrimental impact on the activities of daily living involving postural changes and transfers. Even if AOT has only recently been applied in this field, some preliminary evidence has been provided on its potential to improve walking speed, gait dynamic, and balance parameters in stroke patients [136–144] (see also Patel, 2017 for a recent review[145]).

As AOT effectiveness mostly relies on the activation of cortical territories overlapping across action observation, motor imagery, and action execution, a matter of interest is to evaluate how brain injuries might affect the neural responses to action observation. Especially in unilateral focal brain damage, the critical point is to evaluate how the stroke lateralization may bias the response to action observation. Functional MRI studies in post-stroke patients have investigated this issue. Garrison and coworkers [146] compared 12 right-handed nondisabled participants and 12 left-hemisphere stroke patients during right and left-hand action observation. Action observation elicited the activation of superior temporal, parietal and premotor regions in both groups, with a bilateral pattern in non-disabled participants and a lateralization bias towards the ipsilesional, dominant hemisphere in stroke patients. The reason underlying this bias could relate to the original motor dominance of the left hemisphere and the lateralization of the lesion. While the first study could not resolve this matter, a later study from the same group [147] addressed this issue by enrolling 12 individuals with non-dominant, right hemisphere stroke. This latter group showed a greater response to action observation in the dominant left hemisphere than in the ipsilesional, right hemisphere. This left-lateralized pattern was frequent in stroke patients regardless of the lesion lateralization, suggesting that the original dominance plays a significant role in determining the map of responses to action observation in stroke patients. A summary of these lateralization patterns is represented in Figure 4.

While the above points apply to patients undergoing brain injuries in the adult age, i.e., after the motor system's maturation, a different scenario is relative to unilateral early-onset cerebral palsy, particularly those involving large cortical territories. The case is simpler here since hemispheric dominance is not yet established in children at this age. Thus, motor maps mostly develop in the contralesional primary motor cortex [148, 149], along with the responsiveness to action observation detected over the contralesional fronto-parietal areas [149, 150].

Figure 4. Impact of brain lesions on neural substrates of action observation.
In unilateral and focal damage (e.g., stroke), neural substrates of action observation are differently affected according to the side of the affected hemisphere (dominant vs. non-dominant, i.e., DH vs. NDH). When DH is damaged (top arrow), action observation mainly recruits ipsilesional intact adjacent regions. Conversely, when NDH is involved (bottom arrow), increased contralesional fronto-parietal activity is usually instantiated. (Adapted from Garrison et al. 2013, Liew et al, 2018)



3.2.2 Aphasia

Aphasia affects about 20% of people who suffered from stroke [111]. It represents a remarkable dramatic sequela of cerebrovascular lesions, negatively impacting patients' communication and social skills.

The application of AOT in aphasia should deserve special consideration due to the intimate relationship between spoken language and mirror mechanism substrates. Both processes are neurophysiologically grounded on sensorimotor transformations driving the interplay between a perceiver and an actor. Moreover, they share critical neuroanatomical structures, likely reflecting a common evolutionary root. Indeed, it has been proposed that the ventral premotor cortex (area F5) in monkeys represents the possible homolog neuroanatomical structure of Broca's area in the human brain; this view is supported by topographical analogies (F5 and Broca's area both belong to the inferior portion of Brodmann area 6) and by cytoarchitectonic similarities [151, 152]. These findings led some authors to speculate the theory according to which "*the development of the human speech is a* *consequence of the fact that the precursor of Broca's area was endowed - before speech appearance - with a mechanism for recognizing actions made by others*" [153]. Following this view, such a mechanism would have been the starting point for inter-individual communication and speech development. Given these premises, aphasia may be viewed as a valuable field for AOT application, in which both treatment mechanism and impaired function interact into a common neuroanatomical ground.

However, the AOT studies on aphasia are limited and have been conducted in small samples of patients, impeding the implementation of robust trial designs. The first study involved six not-fluent aphasic patients that underwent an intensive two-week protocol in which the observation of hand actions was followed by their execution and naming attempt. Action observation favored the retrieval fluency of verbs, with clinical benefits persisting at a 2-month follow-up. Subsequent studies [154] confirmed AOT benefits and showed that observed actions had to belong to the patient's motor repertoire to promote verbal retrieval fluency [155]. More recently, neuroimaging studies showed that AOT's ability to improve verbal fluency might be extended beyond verb retrieval, involving other linguistic units [156], as well as picture naming [157].

Based on studies showing that mirror mechanism also transform auditory stimuli into a motor format [72, 158], Zettin et al. [159] recruited seven patients with aphasia that underwent 45 daily sessions in which participants were asked to carefully observe and then imitate six actors pronouncing aloud a series of words and sentences. At the end of the treatment, an overall improvement in linguistic abilities was observed, particularly in repetition and naming. Even if descriptive, these promising findings highlight the opportunity to extend AOT investigations in aphasic disturbances in larger samples of patients, possibly enclosing neuroimaging measures.

3.2.3 Cerebral palsy in children

In the last decades, a growing interest for AOT application in hand rehabilitation for children with CP has emerged, as both a stand-alone treatment [160–164], as well as an add-on intervention associated to other undergoing approaches [165, 166].

In the first pilot study, Buccino et al.[162] randomized 15 children suffering from CP into two groups: children belonging to the first group (experimental group) were asked to observe videoclips of hand actions and then to execute them; those of the second group (controls) were requested to perform the same actions, but following the observation of videos without any motor content. The improvement in hand motor function - as measured with the Melbourne assessment scale [167] - was greater in the experimental group than in the controls. Adopting a similar study design and treatment procedures, Sgandurra et al.

[160] evaluated the efficacy of AOT in improving both a) goal-oriented and b) kinematic parameters of upper limb motor function in children with unilateral CP. The functional improvement involved goal-oriented bimanual skills but not movement kinematics, suggesting that children exploit the mirror mechanism to represent the action goal rather than its kinematics. Evidence that AOT effects on hand motor abilities are determined by brain activity in fronto-parietal networks was provided by a neuroimaging study (Buccino et al., 2018) showing that, following AOT, children with CP display a stronger activation in a parietal-premotor circuit encoding hand-object interactions. These findings have been recently supported by electrophysiological data showing that the motor improvement induced by AOT in children with CP is associated with the post-treatment degree of EEG mu rhythm suppression during action observation [168] (mu rhythm is a reliable index of mirror mechanism activity [169]).

In children with CP, AOT was used as an additional rehabilitation treatment by Simon-Martinez et al. [166] that applied AOT as an add-on to constrained-induced movement therapy (CIMT, see Taub et al., 1999 for a review on this approach[170]), comparing its efficacy with that of the CIMT alone. Even if both groups underwent a significant improvement in hand motor function, the combination of AOT and CIMT resulted in a better outcome for children with more deficient motor functions.

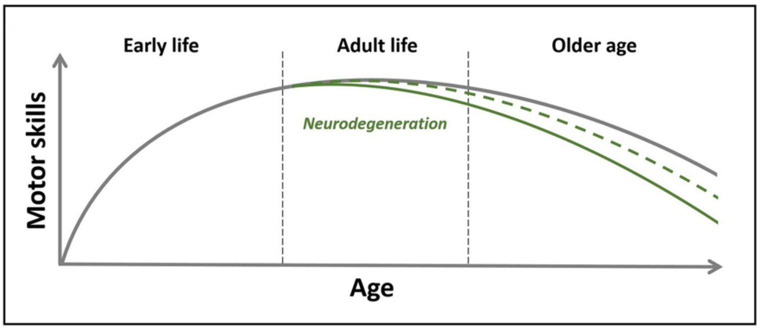
An intriguing aspect intrinsic to AOT is the possibility, especially with children, to design rehabilitative sessions, including peers [165] (see chapter 3).

The effectiveness of AOT in CP children was not confirmed by Kirkpatrick et al [171]. However, such findings must be carefully considered due to the parental, unsupervised administration of AOT. Future, large-sampled investigations will help to detect the predictive factor determining inter-individual differences in clinical responsiveness [166], thus favouring the individualization of AOT and - ultimately – the maximization of its efficacy.

3.3. Neurodegenerative diseases

Clinical and neuroimaging findings from patients with Parkinson's disease [172], amyotrophic lateral sclerosis [173], multiple sclerosis [174], and Alzheimer's disease [175] indicate that AOT may be useful at least in some stages of the disease and counterbalance the functional decline due to neurodegeneration. Such a compensatory gain of function may reflect the recruitment of a *functional reserve*, i.e., the spared capacity of a neural system to counteract the effects of brain dysfunction [176, 177]. Initially adopted in the cognitive domain (i.e., *cognitive reserve,* Stern, 2002), the notion of 'reserve' was later proposed for the motor system (i.e., *motor reserve,* [179, 180]. In this light, AOT in patients with neurodegenerative diseases [172] may be viewed as a strategy to favor motor "plasticity-related recovery within the remaining parts of the damaged network" [177], thus providing resilience to motor skills impoverishment.

Fig. 5. AOT effects on motor skills trajectory in neurodegenerative diseases. Continuous grey line indicates the neurotypical motor trajectory in the absence of any pathological condition. Solid green line shows how trajectories deviate from the original one in the case of neurodegenerative diseases. Dashed line indicates how the administration of AOT modifies pathological trajectories.



3.3.1. Parkinson's disease

Parkinson's disease (PD) is a complex neurodegenerative disorder characterized by both motor and non-motor symptoms. From a systemic viewpoint, PD is thought to reflect dysfunction of networks interconnecting basal ganglia and frontal cortical areas because of the degeneration of the nigrostriatal pathway [181, 182].

While no cure has been found to date, PD is usually treated either pharmacologically (levodopa is currently the "gold standard") or neurosurgically (Deep Brain Stimulation) to reduce the severity of the symptoms. However, none of these approaches prevent PD patients from experiencing a progressive deterioration of their symptomatology, including several motor deficits related to gait, transfers, balance, and posture. In most cases, rehabilitation therapies are then used as an adjuvant to pharmacological and neurosurgical treatments to maximize functional ability and minimize secondary complications.

Aside from motor deficits, the presence of cognitive deficits has been extensively documented and often assimilated to frontal type executive dysfunctions [183], including deficits in verbal fluency [184], working memory [185] and attention both in the early and moderate stages of the disease [186]. The low sensitivity of these deficits to dopamine-related treatments (as well as to other pharmacological approaches) make them difficult to manage with current pharmacological medications [187–189], which are thus mainly directed at motor dysfunctions.

Several rehabilitative approaches aim to teach patients to use compensatory attentional/cognitive strategies that may rely on the recruitment of alternative motor circuits. Indeed, it has been demonstrated that both cueing strategies (based on the use of external stimuli associated with the initiation and facilitation of motor activity) and attentional strategies (such as instructions that rely on cognitive mechanisms of motor control and are internally generated) can improve walking performance [190].

In this sense, motor imagery (MI) and action observation (AO) are promising approaches in rehabilitative treatments for patients with neurological disorders, including PD [191–197]. The neural processes underlying AO and MI involve an extensive cortical-subcortical network, including a wide range of regions contributing to action execution (see Figure 1). Of note, beyond the cortical territories already detailed in the introduction, also basal ganglia [198, 199] and cerebellum [200, 201] are recruited during AO, and the same happens during MI [202, 203].

The first evidence study about action observation in patients with PD dates back to 2010. Pelosin and coworkers [204] showed that a 4-week training based on AO, combined with practicing the same actions, could reduce freezing-of-gait episodes in patients with PD relative to an equal treatment based on static landscapes observation. These results were confirmed and strengthened by a later study from the same group [205]. Sixty-four participants with PD and freezing-of-gait were assigned to the AOT or control groups and underwent a 45-minute training session, twice a week, for five weeks. AOT consisted of physical training combined with action observation, whereas the control group executed the same physical training combined with landscape-videos observation. The large test battery used to evaluate the efficacy of the intervention (FoG questionnaire, Timed Up and Go test, 10-meter walking test, and Berg balance scale) indicated how both groups took advantage of the training, showing an increase of all scores at the end of the training relative to the baseline. However, most of these improvements were retained at a 4-week follow-up only in the AOT group, proving the enhancing effect of AO in PD motor rehabilitation programs.

In a parallel study, Agosta et al. [206] randomized 25 patients with PD and freezing-of-gait in 2 groups (AOT and control), confirming that AOT leads to a reduced motor disability and improved balance. In addition, they recorded fMRI both at baseline and the end of the training (4-weeks) during different tasks, including the observation and the motor imagery of three actions typically exacerbating freezing-of-gait, i.e., starting and stopping walking in a narrow hallway, turning around 360° in a small radius, and going through a doorway. Contrasting fMRI at the end of the training against the baseline, the AOT group showed increased recruitment of fronto-parietal areas during fMRI tasks in cortical territories known to be recruited by both the execution and the observation of walking actions [16, 207]. Conversely, the control group witnessed a widespread reduction of fMRI activity over peri-rolandic and parietal regions. Of note, the fronto-parietal increase observed at 4-weeks resulted predictive for the clinical evolution at 8-weeks, reinforcing the notion that AOT has a more long-lasting effect in improving motor function in PD patients.

The benefits induced by AOT in patients with PD may not be limited to freezing-of-gait, but previous studies extended the impact to a reduction of bradykinesia [208], to saccadic eye movements [209], balance [206, 210], and up to cognitive functions like verbal and visuospatial working memory in the case of dual tasks [212].

Noteworthy, in the case of PD, the choice of first vs. third perspective is still controversial. While some studies showed that the delivery of egocentric stimuli could improve motor deficits [213], others [214] suggested that patients with PD could have difficulties in egocentric motor simulation, partially explaining patient's preference for a third-person perspective when observing actions to be later pantomimed.

3.3.2. Multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system and represents the first cause of non-traumatic disability in young adults. About 75% of people with MS experience a motor impairment of upper limbs that negatively impacts the independence in activities of daily living and quality of life [215]. Nevertheless, interventions targeting the upper limbs in MS are limited compared to those concerning lower limbs function in MS and upper limbs in other neurological conditions (e.g., stroke). In the last two decades, neuroimaging investigations on neural substrates of action observation and execution in MS paved the way to implementing pilot AOT protocols to improve upper limb motor function in this clinical field.

The first study enquiring mirror mechanism in MS [216] showed that - in comparison to healthy individuals – these patients have higher activation in fronto-parietal circuits endowed with mirror properties during both action observation and action execution. Such an increased activity - even if poorly detectable in the first stages of the disease [217] - has been interpreted as compensatory recruitment of pre-existing latent pathways able to promote cortical adaptation to MS-related brain damage. Based on this point, previous studies speculated that brain areas endowed with the mirror mechanism might also evolutionarily supply a functional-motor reserve to be dedicated to action execution in case of malfunction of other motor areas [216].

To exploit the potentiality of AOT to promote motor recovery in MS and to investigate its neural substrates, Rocca et al. [174] assessed the brain functional and structural changes following AOT in MS. In this clinical-neuroradiological study, 41 patients suffering from MS with dominant-hand motor impairment and 26 healthy controls were randomized to AOT (i.e., watching action-related videos and then action execution) or control training (watching landscapes videos and then action execution). After a training period of 2 weeks, patients with MS - especially in the AOT group - improved upper limb functions. Moreover, AOT performed in the MS group induced structural changes in fronto-temporal areas. From a functional perspective, patients with MS undergoing AOT displayed modifications in the recruitment of areas endowed with mirror mechanism and their connectivity.

Interestingly, hand-motor improvement is correlated with structural and functional MRI modifications in motor areas (e.g., ipsilateral inferior frontal gyrus) involved in action observation/action execution matching system. Even if only recently undertaken in MS, the use of AOT showed promising results for the amelioration of motor symptoms. Another non-negligible aspect is that MS motor rehabilitation lasts for a lifetime, and thus the adaptability of AOT to portable settings could represent a significant factor in alleviating the rehabilitative load of MS patients.

3.4 Systematic reviews on action observation treatment

Concerning the rehabilitative field, previous systematic reviews and metanalyses quantified the efficacy of Action Observation Treatment in neurological conditions as stroke [218–221, 221, 221–223], Parkinson's disease [188, 194, 222], Cerebral Palsy [219, 222, 224, 225] and Multiple sclerosis [222], as well as in musculoskeletal conditions [222].

The level of evidence for motor benefits from AOT delivery is strong for Parkinson's and Stroke populations [219, 222], moderate for orthopaedic and multiple sclerosis patients [222], and small-to-moderate for children with CP [219].

It is worth mentioning that most of the studies conducted to date on AOT applied heterogeneous procedures in terms of posology (from a single session to several weeks), visual features of the stimuli (person-related and viewing perspectives, 2D vs. 3D), motor features of the represented actions (transitive or intransitive actions, kinematics), administered task (association or not with motor imagery or imitation) and outcome measures. Such a variety prevents identifying the optimal AOT parameters [194, 222], especially considering that they might substantially vary across different clinical conditions, and advocates for further randomized-controlled trials testing large samples with reliable AOT procedures.

3.5 Looking for the *crystal ball* on AOT outcome

Another factor explaining AOT outcome heterogeneity may rely on the presence of subject-specific features affecting the chance to properly respond to the treatment. In this context, the identification of neurophysiological predictors determining individual response to treatment, represents a major challenge for the optimization of AOT pathways. At the same time, the detection of such biomarkers may help to unravel the mechanism underlying AOT efficacy.

In the next chapter, experimental findings in this field will be presented.

Chapter 1

Electrophysiological features predicting motor skill improvement by action observation.

This chapter is based on the article: *"Electrophysiological features predicting motor skill improvement by action observation".* Nuara A., Bazzini M.C., Rizzolatti G., Fabbri-Destro M., Avanzini P. *Under review on Brain Stimulation*

1. Introduction

Action observation plays a key role in promoting neuroplasticity processes underlying motor learning [22, 35, 226, 227]. Following this principle, a motor training approach grounded in the alternation of action observation and execution (i.e., action observation training [AOT]) has been developed to promote the acquisition and recovery of motor abilities [227].

The transformation of sensory representations of others' actions into one's motor representation (i.e., mirror mechanism [228]) represents a key process by which AOT may lead to behavioral effects. Indeed, at the neurophysiological level, action observation affects the excitability of the motor system, which can be measured by transcranial magnetic stimulation (TMS), assessing corticospinal excitability [229–231], intracortical inhibition [230, 232, 233], and transcallosal inhibition [234] (see also Naish et al. [235]). However, whether these corticomotor modulations evoked by action observation explain the individual amount of motor improvement driven by AOT remains to be addressed.

For this purpose, we evaluated, via TMS, the effects of action observation on (1) corticospinal excitability (motor evoked potentials [MEPs]), (2) short-interval intracortical inhibition (sICI), and (3) transcallosal inhibition (ipsilateral silent period [iSP]) in 40 healthy participants. Subsequently, we administered either an AOT or, as a control, motor training with observation of non-action videos. Finally, we assessed the capacity of each neurophysiological marker to predict AOT outcomes. The identification of predictors sheds light on the cortical mechanisms underlying AOT efficacy and sets the premises for developing assessments aimed at identifying the best candidates for AOT.

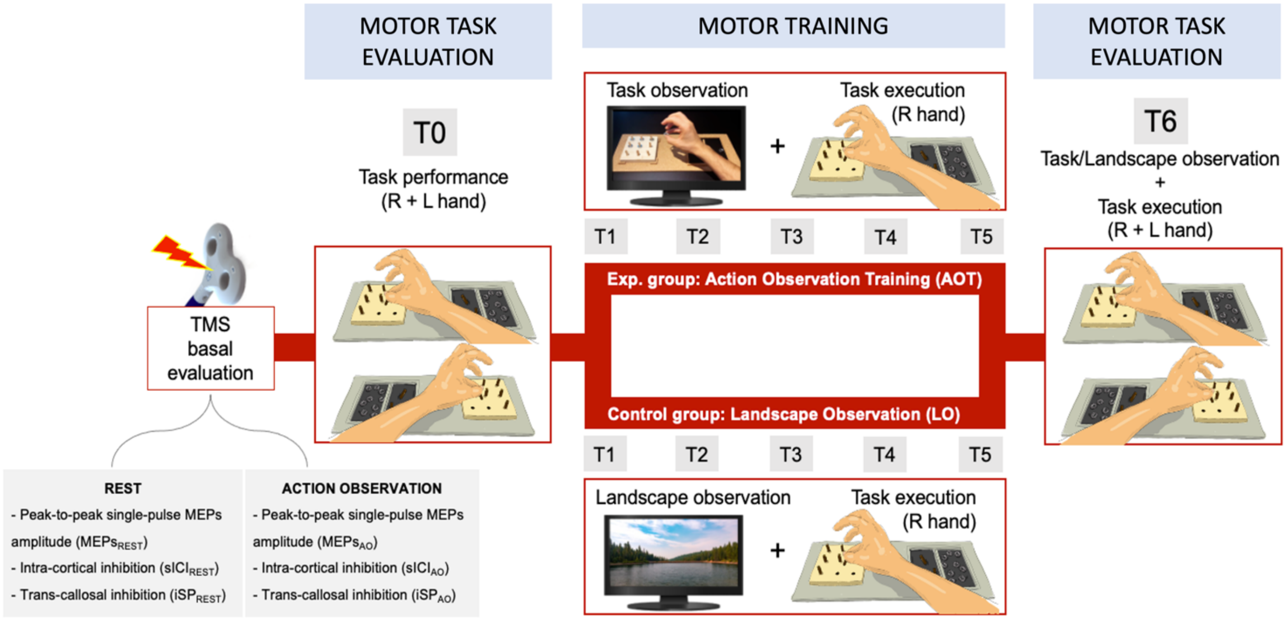
2. Methods

2.1 Participants

Forty subjects (10 males and 30 females, mean age 36 ± SD 9 years [range 22–61 years]) were recruited for the study. All subjects were right-handed, as assessed by the Edinburgh Handedness Inventory [236]. None of them had any history of neurological/psychiatric diseases or contraindications to TMS administration [237]. Participants were informed about the experimental procedures and gave their written consent according to the Helsinki Declaration. The experiment was approved by the local ethical committee “Area Vasta Emilia Nord” (n. 10084, 13.03.2018).

In the next paragraphs, we will detail the experimental design, which is graphically summarized in Figure 1.

Figure 1. Study design.
In the first phase (i.e. *baseline evaluation*), corticospinal excitability modulation by action observation, and bilateral hand motor performance, were assessed (T0). In the second phase, participants were randomized into two groups. AOT subjects were asked to observe a video clip showing a correct execution of the mNHPT, then to execute it as quickly and accurately as possible. Such observation-execution combination was repeated six consecutive times (T1-T6). The last trial (T6) also included the left-hand mNHPT execution. Participants of the control, landscape-observation group (LO) followed the same procedure of the experimental group, except for the the video clip preceding the mNHPT execution, depicting an animated lake landscape. mNHPT performance was recorded across T0-T6 timepoints.



2.2. Baseline evaluation

TMS was delivered by a figure-of-eight coil (70 mm) connected to a Magstim BiStim stimulator (Magstim, Whitland, UK) and combined with electromyographic (EMG) measurements to assess MEPs. TMS was applied to the scalp, with the coil handle rotated 45° from the sagittal plane. Before the experimental session, the optimal stimulation location (hotspot) corresponding to the right first digital interosseous (R-FDI) was determined. The hotspot was defined as the scalp location providing the highest peak-to-peak MEP amplitude in the relaxed R-FDI averaged over five consecutive stimuli. The coil position and orientation were coregistered to a brain template obtained from individual head landmarks (nasion, ears, scalp surface) using an optoelectronic neuronavigation system (visor 2, ANT Neuro, Netherlands).

EMG signals from the R-FDI muscle and the left opponens pollicis (L-OP) were continuously recorded using surface Ag–AgCl electrodes. The EMG signal was amplified (×1000) using a CED1902 amplifier (Cambridge Electronic Design), sampled at 2.5 kHz, filtered with an analogical online band-pass (20–250 Hz) and a notch (50 Hz) filter, and acquired with CED Micro 1401 interfaced with Spike2 software (Cambridge Electronic Design). An additional channel containing digital markers of the TMS trigger was integrated into the same EMG file. The data were stored for subsequent analyses.

The corticomotor excitability was assessed with the following TMS parameters:

a) The resting motor threshold (RMT), defined as the lowest stimulator output intensity capable of inducing MEPs greater than 50 μV peak-to-peak amplitude in relaxed R-FDI in at least 5 of 10 trials [238].

b) Peak-to-peak amplitude of MEPs elicited in the resting R-FDI by single-pulse TMS (120% RMT intensity).

c) sICI was obtained from a paired-pulse TMS protocol [239]. A subthreshold conditioning stimulus was delivered at 80% of the RMT and at an interstimulus interval of 3 ms before a suprathreshold, conditioned, test stimulus (120% RMT). Both stimuli were delivered by the same coil in the same scalp position. sICI was expressed as the percentage decrease of MEP amplitude relative to the single-pulse TMS condition, according to the following formula: $sICI = \left(1 - \frac{Conditioned\ MEP\ amplitude}{Single\ pulse\ MEP\ amplitude}\right) * 100.$

d) iSP was acquired by delivering single-pulse TMS to the right opponens pollicis hotspot (obtained with a procedure like that described for the R-FDI muscle) while the participant maintained a maximal contraction of the L-OP.

The iSP parameters were computed from the rectified traces of the L-OP EMG. The iSP onset was defined as the point at which EMG activity decreased (minimum duration 10 ms) of at least 2 standard deviations relative to the baseline (60-10 ms prestimulus). The iSP offset was defined as the first point after iSP onset at which the EMG activity regained the baseline value. The iSP_{AREA} was defined as the EMG area between iSP offset and iSP onset, while $Baseline_{AREA}$ as the EMG area between 60-10 ms before the TMS stimulus [240]. We then calculated the iSP amount according to the formula:

$$iSP_{AMOUNT} = \left(1 - \frac{iSP_{AREA}}{Baseline_{AREA}}\right) * 100 \text{ [241].}$$

Subjects performed the experiment seated in a comfortable armchair and in front of a 17-inch LCD computer monitor (1024 x 768 pixels) placed 60 cm from their frontal plane. First, the abovementioned TMS parameters were measured during the continuous observation of a black screen with a white cross in its center (REST). Three separate sessions lasting two minutes were administered, one for each specific TMS parameter (standard MEPs, sICI, and iSP). While subjects were asked to keep their upper limbs relaxed during standard MEPs and sICI assessments, during the iSP assessment, they were requested to start the voluntary contraction upon the verbal request of the experimenter, who controlled and jittered the delivery of TMS pulses. Within each session, 15 TMS pulses were administered.

After the REST protocol, the same parameters listed above were estimated during action observation. In this protocol, subjects were asked to carefully observe 24 video clips depicting reach-to-grasp actions toward different objects. Each video, showing a pinch- or tri-digital grasp, represented the action from a first-person perspective and lasted 3.5 s. An intertrial (2 s, black background) was interposed between the videos. The overall action observation trial duration was about 2 minutes, in line with the resting condition. During the iSP assessment, subjects were requested to start the voluntary contraction at each action onset and to relax during the intertrial. Within each session, in 15 of the 24 videos, TMS was randomly delivered 200 ms prior to hand-object contact. Such a latency has been previously shown as the timepoint providing the maximal MEP amplitude [231, 242]. Considering potential repetition suppression phenomena related to the TMS series [243], the protocol sequence was randomized across participants.

2.2. Motor training

A modified version of the Nine Hole Peg Test (mNHPT)—a quantitative test of upper extremity function [244]—was adopted to assess motor performance. Previous studies have shown that the performance of the standard NHPT strongly depends on frontoparietal network functioning [245] [246]. Moreover, NHPT performance improves with repetition over time [247], denoting the test's suitability as a motor learning endpoint. At baseline (T0), both the right and left hands were tested (see Figure 1, task performance). Participants were seated at a table hosting a woodblock with nine empty holes on one side and a small container on the other. The latter was further split into two parts holding nine pegs and nine nuts, respectively.

On a start cue, subjects had to pick up the nine pegs one at a time as quickly as possible and put them in the nine holes according to a preestablished order (left to right, top to bottom). After placing the pegs in the holes, they had to apply the nuts in correspondence with each peg, following the same insertion order. Finally, they had to remove the nuts and pegs as quickly as possible—one at a time, placing them back into the proper container. Noteworthy, subjects were asked to adopt a first–fifth pinch grasp (thumb–little finger) throughout the task. This constraint, as well as the adding of the nuts, was introduced in the modified version of the test to increase task difficulty, thus delaying the performance "ceiling effect." The task was video-recorded and scored offline. The time required to perform the mNHPT was selected as the primary endpoint. In addition, errors, defined as placing, sequence, or hand-posture inaccuracies, were registered.

Subjects were randomized into two groups (see upper and lower strips in Figure 1). Participants belonging to the experimental (AOT) group (n = 20) were asked to observe a video clip showing a correct right-hand execution of the mNHPT (duration 1:16 min) and then to execute it as quickly and accurately as possible. This observation-execution combination was repeated six consecutive times (namely, T1–T6). The last trial (T6) also included left-hand mNHPT execution, thus allowing a direct before and after training comparison of both hands' performance. Participants in the control (landscape-observation) group (n = 20) followed the same procedure, except the content of the video clip preceding the mNHPT execution depicted a landscape.

The time required to perform the mNHPT was recorded at each timepoint. The percentage decrease of total time relative to T0 (in other words, the increased speed) was computed. The T0–T6 percentage difference in right-hand mNHPT execution speed was set as the main behavioral endpoint. Secondary endpoints included T0–T6 left-hand improvement in mNHPT execution speed.

2.3 Data analysis

The effect of action observation on motor cortex excitability was assessed by comparing the TMS parameters (MEPs, sICI, iSP) between the *rest* and *action observation* protocols by means of direct, nonparametric contrasts (Wilcoxon test). The choice of nonparametric tests was due to the absence of normality assumption.

Beyond investigating the modulations induced by action observation at the population level, we also moved to the individual level, thus computing the ratio between action observation and REST protocols for each of the TMS parameters:

a) $\text{MEPs}_{(\text{AO})}/\text{MEPs}_{(\text{REST})}$
b) $\text{sICI}_{(\text{AO})}/\text{sICI}_{(\text{REST})}$
c) $\text{iSP}_{(\text{AO})}/\text{iSP}_{(\text{REST})}$

Mixed ANOVA was applied to the right-hand mNHPT speed increase, considering TIME as a within-subject factor and GROUP as a between-subjects factor. As T0 served as a baseline for individual data, six levels were included in TIME (T1–T6). Planned comparisons were made using independent sample, two-tailed t-tests, limited to the comparison between groups at each timepoint.

Subsequently, the correlation between the basal neurophysiological features assessing left-hemisphere excitability modulation by action observation ($MEPs_{(AO)}/MEPs_{(REST)}$, $sICI_{AO}/sICI_{REST}$) and motor outcomes (right- and left-hand T0–T6 mNHPT improvement) was separately evaluated in each group using Spearman's rank correlation. iSP_{AO}/iSP_{REST} was correlated with left-hand T0–T6 mNHPT improvement only.

In case of significant correlations, the capability of the neurophysiological modulations induced by action observation to predict motor improvement in subjects undergoing AOT was tested by applying a linear regression model. In case of multiple significances, multiple linear regression models were also applied to evaluate the cross-talk between individual regressors. For each significant regression, a Bayesian factor ($BF_{1|0}$) was computed to quantify the evidence in favor of the alternative hypothesis (i.e., the neurophysiological feature *predicts* motor outcome) relative to the null hypothesis (i.e., the neurophysiological feature *does not predict* motor outcome).

Despite being widely adopted and easy to interpret as a motor learning endpoint, the mere difference between T0 and T6 does not account for the temporal dynamics of the learning process. Indeed, regardless of the T6 performance, the learning curve at T6 could exhibit higher/lower slopes. Thus, for each subject, we applied a regression model to fit the timewise performances into a logarithmic curve defined by the following equation: $y = A * \log(bx)$, where x indicates the trial number and the A coefficient indexes the slope of the curve. In the case of significant regression, the A coefficient can be regarded as a time-independent index of *motor learning drive*. Significant results would extend the validity of timepoint-specific observations to a global, time-independent dynamic. Then A values were compared between groups by direct contrast (independent samples, two-tailed t-test), and following the same statistical procedures described above, a linear regression was performed against baseline neurophysiological variables.

3. Results

3.1 Participants' compliance and safety

All the experimental procedures were well tolerated. In particular, no side effects related to TMS administration were reported. One subject did not complete the experimental procedures, even though she completed the baseline neurophysiological evaluation.

Concerning sICI, one control subject was excluded from the neurophysiological evaluation due to the triggering system malfunctioning.

3.2 Participants' baseline features

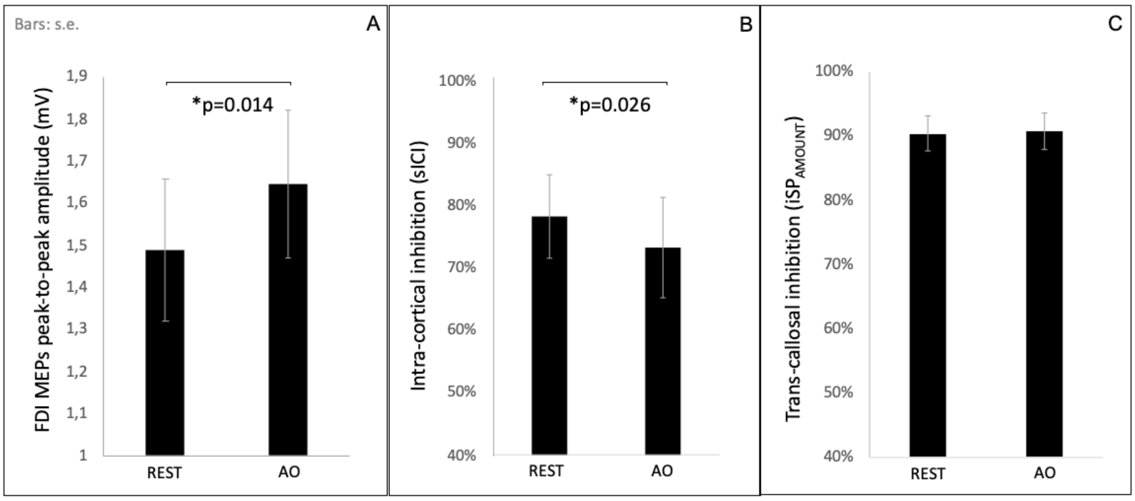
An independent samples t-test did not detect significant between-group differences in baseline behavioral and neurophysiological features (right mNHPT: t[39] = −0.762, p = 0.45; left mNHPT: t[39] = −0.240, p = 0.81; RMT: t[39] = 0.115, p = 0.91; MEP amplitude: t[39] = 0.66, p = 0.512; sICI: t[39] = 1.870, p = 0.70; iSP: t[39] = 0.708, p = 0.48).

3.3 Effect of action observation on corticomotor excitability

Single-pulse MEPs elicited during action observation were significantly higher than during the resting condition (1.46 ± 1.06 vs 1.65 ± 1.09 mV, Z[40] = 2.460, p = 0.014, see Figure 2, Panel A), indicating an average facilitation effect of 13%. Although the overall effect was significant, a consistent variability emerged at the single-subject level; 14 out of 40 subjects (35%) showed a decrease in MEP amplitude during action observation.

Action observation induced a significant decrease in sICI (78.25% ± 20.95% vs. 73.26% ± 25.00%, Z[39] = −1.619, p = 0.02, Figure 2, Panel B). Even in this case, despite the overall significant decrease, 13 out of the 39 participants (32%) displayed an increase in sICI during action observation. A little overlap (n = 1) was observed between the 14 MEP suppressors and the 13 sICI enhancers. No significant change was observed comparing ISP amount at rest vs. during action observation (90.47% ± 27.35 vs 90.88% ± 28.63 p = 0.35, see Figure 2, Panel C).

Figure 2.
Effect of action observation on peak-to-peak MEPs amplitude (panel A) and short-interval intra-cortical inhibition (sICI, panel B) and trans-callosal inhibition (ISP_{AMOUNT}, panel C). Bar charts represent the mean value of neurophysiological variables in the overall population at rest and during action observation (AO).



3.4 Effect of action observation on motor improvement

Repeated measure ANOVA showed that both TIME (F [5, 185], $p<0.001$) and GROUP (F [1, 37], $p<0.001$) factors had a significant effect on mNHPT speed. Planned contrasts indicated that subjects undergoing AOT had greater improvement than controls since the first execution and throughout all the timepoints (see Figure 3, Panel A). No significant time*group interaction was found. The main motor outcome—that is, overall improvement at T6 in right-hand mNHPT speed—was greater in AOT subjects in comparison to controls (27.67% ± 6.4 vs. 19.01% ± 3.1; t[39] = −5.362; $p<0.001$; $\eta^2 = 0.437$). There were similar findings regarding left-hand mNHPT performance at T6 (controls 14.55% ± 7.95 vs. AOT 20.01% ± 7.16; t[39] = −2.288; $p = 0.028$; $\eta^2 = 0.124$; see Figure 4, Panel A).

3.5 Neurophysiological predictors of motor improvement

To investigate whether the TMS features evoked by action observation were associated with the motor improvement promoted by AOT, the MEP amplitude gain in response to action observation ($MEPs_{(AO)}/MEPs_{(REST)}$) and the relative increase in intracortical inhibition during action observation ($sICI_{(AO)}/sICI_{(REST)}$) were correlated with the improvement in right- and left-hand mNHPT speed, separately for the two groups.

In the AOT group, right-hand improvement was positively correlated with $MEPs_{(AO)}/MEPs_{(REST)}$ ($\rho = 0.629$, $p = 0.003$) and $sICI_{(AO)}/sICI_{(REST)}$ ($\rho = 0.733$, $p<0.001$). Linear regression showed that both $MEPs_{(AO)}/MEPs_{(REST)}$ ($R^2 = 0.304$, $p<0.001$) and $sICI_{(AO)}/sICI_{(REST)}$ ($R^2 = 0.604$, $p<0.001$) constituted significant predictors of the right-hand motor improvement following AOT (see Figure 3, Panel B). The multiple linear regression model confirmed the stronger predictive value of $sICI_{(AO)}/sICI_{(REST)}$ in comparison to $MEPs_{(AO)}/MEPs_{(REST)}$ ($R^2 = 0.624$ vs. $R^2 = 0.339$, $p<0.001$) but also indicated their combination as the best predictor of right-hand motor improvement ($R^2 = 0.680$, $p<0.001$). Bayesian factors confirmed a lower level of evidence for $MEPs_{(AO)}/MEPs_{(REST)}$ ($BF_{1|0} = 5.64$) relative to $sICI_{(AO)}/sICI_{(REST)}$ ($BF_{1|0} = 312.01$) and their combination ($BF_{1|0} = 234.33$), both indicating a decisive level of evidence [248].

Moving to the left hand, a positive correlation between motor improvement and only $MEPs_{(AO)}/MEPs_{(REST)}$ was found ($\rho = 0.547$, $p = 0.012$). A subsequent linear regression model identified $MEPs_{(AO)}/MEPs_{(REST)}$ as a predictor of motor improvement.($R^2 = 0.366$, $p<0.01$, see Figure 4, Panel B). Here, the correspondent Bayesian model returned a $BF_{1|0}$ of 5.193, indicating a substantial level of evidence [248] in favor of the alternative hypothesis. It is worth noting that the correlational analyses involving the controls did not return any significant results (see Panel C of Figures 3 and 4), supporting that the AOT motor outcome is specifically associated with the effect of action observation on MEPs and sICI.

3.6 Regression fitting model

Individual data of right-hand performance were fitted with a logarithmic model ($y = A * \log(bx)$, where x indicates the trial number [see Methods]). Subjects' curves showed excellent fitting values (all $p<0.05$), with adjusted R^2 ranging from 0.605 to 0.960 (mean $R^2 = 0.833$). The comparison of A coefficients between groups showed higher values in AOT subjects than in controls ($t[39] = -3.785$; $p<0.001$; $\eta^2 = 0.279$), supporting that AOT biases the whole motor learning trajectory beyond the single timepoints.

In line with the previous analysis, a linear regression was tested between the estimates of the A coefficient and neurophysiological features. Both $\text{MEPs}_{(\text{AO})}/\text{MEPs}_{(\text{REST})}$ ($R^2 = 0.329$, $p<0.001$) and $\text{sICI}_{(\text{AO})}/\text{sICI}_{(\text{REST})}$ ($R^2 = 0.575$, $p<0.001$) were significant predictors of A, thus extending the predictive power of such neurophysiological signatures on time-independent AOT outcome.

Figure 3.

Right-hand motor improvement induced by AOT and neurophysiological predictors of efficacy.

Panel A. Right-hand mNHPT variations across evaluation timepoints in action observation training (AOT, red lines) and control group (grey lines). Single-subject learning trajectories and mean values are respectively represented in thin and thick lines.

Panel B. Scatterplot showing the interplay between right-hand mNHPT T0-T6 improvement in AOT group and: (1) MEPs amplitude gain induced by action observation (top), (2) Intra-cortical inhibition (ICI) relative increase during action observation (bottom). Note the significant positive correlations and regressions.

Panel C. Scatterplot representing the same variables of panel B in the control group. Here, no significant correlations were found.

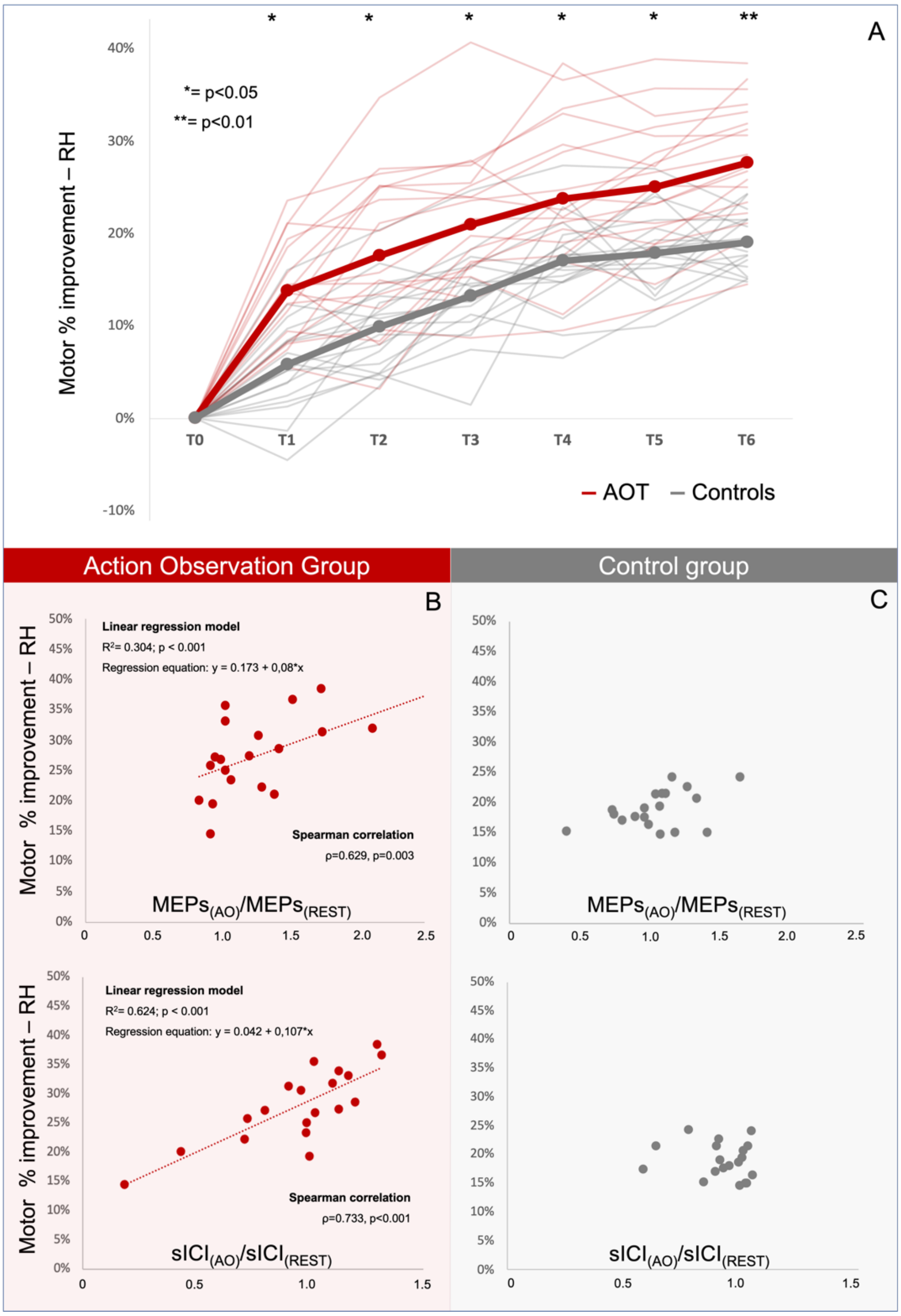
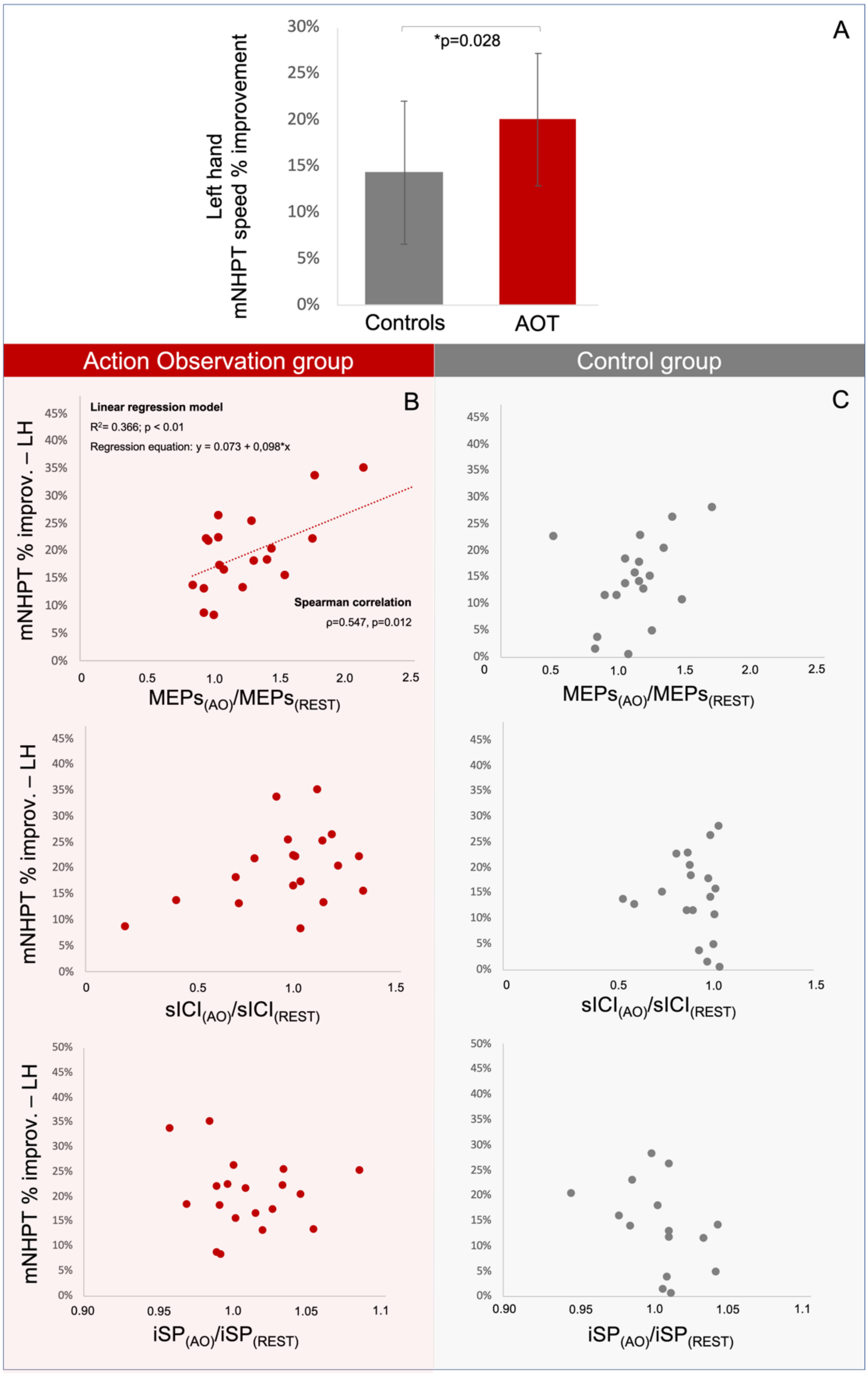


Figure 4.
Left-hand motor improvement induced by AOT and neurophysiological predictors of efficacy.
Panel A. Left-hand mNHPT T0-T6 change between two groups.
Panel B. Scatterplot showing the interplay between left-hand mNHPT T0-T6 improvement in AOT group and: (1) MEPs amplitude gain induced by action observation, (2) Intra-cortical inhibition (ICI) relative increase during action observation, (3) Inter-hemispheric inhibition (iSP) relative increase during action observation. MEPs amplitude gain induced by action observation and left-hand motor improvement resulted significantly correlated.
Panel C. Scatterplot representing the same variables of panel B, in control group.



4. Discussion

In this study, we aimed at identifying the neurophysiological signatures explaining motor improvement induced by AOT. We first collected TMS measures assessing the effects of action observation on corticomotor excitability. Then, in a subsequent randomized-controlled experiment, we demonstrated the superiority of AOT relative to motor practice in driving motor learning. Finally, we proved that the modulation of (1) corticospinal excitability and (2) intracortical inhibition induced by action observation successfully predicts individual susceptibility to AOT.

4.1 Action observation effect on corticomotor excitability

One of the simplest ways to probe corticospinal excitability is delivering a single pulse of suprathreshold TMS on a cortical motor map while recording, at the corresponding muscular level, the evoked motor potentials (MEPs), whose amplitude reflects the amount of activated cortical and spinal motor neurons. Consistent with previous reports [229, 230, 235], we found that action observation enhances corticospinal excitability, as measured by MEP amplitude. Three, not mutually exclusive, anatomical models can be adopted to explain such motor-output facilitation. First, the enhancement of primary motor cortex excitability may be driven by excitatory cortico-cortical projections from the premotor [249] and parietal [250] areas. Second, direct [251] descending projections from premotor areas endowed with a mirror mechanism to the spinal cord may increase the pool of recruited spinal motoneurons, resulting in higher MEP amplitude. Third, cortico-striatal neurons endowed with a mirror mechanism may modulate the corticospinal gain, in line with previous findings in animal models [252, 253]; future investigations combining TMS with the administration of pharmacological dopaminergic modulators during action observation will help to validate this hypothesis.

While MEP amplitude is related to the number of corticospinal neurons activated at a given stimulus intensity [254], paired-pulse TMS measure of intracortical inhibition (sICI) reflects the excitability of distinct, low-threshold, GABAergic interneural circuits within the motor cortex [239, 254–257]. Even with a remarkable interindividual variability, we found that action observation, overall, provokes a transient downregulation of corticomotor inhibitory circuits. This result is in line with previous research, where sICI decrease has been related to action observation [230, 258], joint action [232], and action mistake observation [233].

Conversely, we did not find modulation of interhemispheric inhibition during action observation, in partial contrast with a previous report [234]. Methodological differences, such as the use of video clips instead of a live actor, as well as the absence of EMG-based dynamical TMS triggering, could have determined such divergences in results.

It is worth noting that a relevant proportion (35%) of participants showed suppression of MEP amplitude during action observation. Although surprising, this finding is consistent with previous studies [259, 260] and is not incompatible with the neurophysiological models above. Indeed, it could be envisioned a *"behavioral strategy"* view [235, 261, 262] where the excitability of motor pathways is first enhanced by action observation but subsequently suppressed to a greater extent by inhibitory projections from the prefrontal cortex and inferior frontal gyrus [263–265], when subjects requested to volitionally refrain from movement would "repress the urge to act" [261, 262].

Another interpretation is that the decrease in MEP amplitude could reflect an action observation–induced inhibitory activity of interneurons hosted in the primary motor cortex [235]. However, the notion that MEP suppressors do not correspond to sICI enhancers and the absence of a correlation between MEP suppression and sICI during action observation make this latter perspective less likely.

4.3 **Electrophysiological predictors of action observation training efficacy**

A huge body of research indicates that action observation can help empower existing motor competencies, especially for motor skills requiring fine control [227]. Here, we experimentally confirmed that AOT improves hand motor skills, even in the limb contralateral to that observed and actively practiced. Such an improvement is predicted by the modulations induced by action observation on corticospinal excitability—that is, the greater the MEP facilitation during action observation, the greater the motor skill improvement induced by AOT.

From a neurophysiological perspective, we could speculate that the neural mechanism transiently ignited by action observation could result in neuroplasticity changes, leading to better AOT outcomes. Supporting this view, it has been recently demonstrated that the synaptic efficiency potentiation of premotor-to-M1 connections—a key neuroanatomical pathway underlying motor facilitation *via* mirror mechanism [228, 250, 266, 267]—determines the improvement of NHPT performance [246]. An alternative, complementary view is that the repetitive activation of pyramidal tract neurons from premotor areas projecting to the spinal cord may induce spinal plastic changes [268] associated with hand motor control improvement [269]. Interestingly, the predictive role of right-hand muscle facilitation evoked by action observation extends to the left-hand AOT-induced improvement, consistent with the acknowledged bi-hemispheric recruitment of sensorimotor areas during the observation of unimanual actions [20].

Motor tasks' speed and accuracy depend on the proper selection of which muscles *to move* and which ones *not to move* in each action instant—that is, the appropriate balance between muscle excitation and inhibition [262]. This capacity is even more crucial when dealing with visuomotor tasks [270], precise hand movements [271], and tool use [272]. Moreover, GABAergic cortical activity drives *surround inhibition*, a mechanism that increases the level of segregation of motor activity [273]. TMS measures of intracortical inhibition may constitute a valuable, indirect index of such motor selectivity [270, 273, 274]. We found that the modulation of sICI by action observation largely predicts AOT efficacy, explaining more than 60% of its variance; specifically, subjects with higher increases in intracortical inhibition during action observation showed outperforming AOT learning curves. The evidence in favor of this relationship is strong, more than three hundred times more likely than the *no link* hypothesis.

Recent findings have shown that visuomotor properties in the action observation network might be represented by cell classes that include inhibitory interneurons [275]. We propose that the ability to upregulate such inhibitory circuits in response to action observation may favor the instantiation of inhibitory motor engrams [226], ultimately improving the executive control of the correspondent motor program.

The identification of electrophysiological signatures explaining AOT efficacy may represent the *experimental prelude* to the development of predictive assessments for the selection and identification of the best candidates for AOT in rehabilitative settings and motor training contexts. Extending such knowledge to clinical frameworks would help clinicians to improve the accuracy of prognoses and tune treatment plans, ultimately optimizing patients' rehabilitation pathways. In this framework, it is worth noting that TMS parameters may be abnormal in several common neurological diseases [240, 276], and future investigations applying our procedures to specific neurological conditions must be envisioned.

4.4 Conclusion

Here, we identified, for the first time, the electrophysiological signatures predicting AOT outcome. Among them, intracortical inhibition modulation plays a major role. We advance that, rather than a volitional "hand-brake" on undesired motor output, the upregulation of such inhibitory mechanisms via action observation may play a key role in the fine-tuning of motor programs, ultimately improving the correspondent performance. Besides its theoretical significance, our study could pave the way for the development of neurophysiological models predicting AOT outcome at the individual level, answering the current need to optimize the rehabilitative pathway of multiple clinical conditions.

Chapter 2

Efficacy of a home-based platform promoting child-to-child interaction on hand motor function in children with unilateral cerebral palsy

This chapter is based on the article: *"Efficacy of a home-based platform for child-to-child interaction on hand motor function in unilateral cerebral palsy"*. Nuara, A., Avanzini, P., Rizzolatti, G. and Fabbri-Destro, M. (2019), Dev Med Child Neurol, 61: 1314-1322

1. Introduction

Cerebral palsy (CP) describes a group of permanent disorders regarding the development of movement and posture attributed to non-progressive disturbances occurring in the developing fetal or infant brain[277]. With an incidence rate of 2 to 3 per 1000 live births, CP represents the most common cause of childhood chronic physical disability[278]. Children with unilateral cerebral palsy (UCP) - 30%-40% of the overall population of children with CP - might experience predominant upper-limb motor impairment that negatively affects their quality of life [279, 280].

Treating the physical aspects of the disability is as important as addressing both children and parent's emotional and recreational needs. Indeed, CP management is challenging and should aim to promote a child's social and emotional development, as well as the problems linked to communication, mobility, and independence in activities of daily living (ADL) [280–282]. Due to the fundamental role of hand function in the above-mentioned faculties, and the prevalence of hand-motor impairment in UCP[280, 283], the development of neurorehabilitative strategies aiming to enhance hand motor skills represents a major theme in pediatric neurology.

Targeted upper-limb therapies, such as constraint-induced movement therapy (CIMT), hand-arm bimanual intensive training (HABIT), and other integrated approaches have all emerged in recent decades. Reviews show that intensive approaches in hand motor rehabilitation achieve better improvement of upper-limb function compared to standard treatment methods and that bimanual and unimanual training are similarly effective[284, 285].

To date, neurorehabilitation in children with CP has usually been carried out in clinical settings, with children and parents having to adhere to intensive programs with subsequent relevant costs for both health services and families. Moreover, the insufficient provision of therapeutic services for children with disabilities is an internationally recognized problem. Therefore, alternative service delivery models have been proposed, including family-centered and domiciliary approaches[286–290]. However, such home-based approaches present relevant limitations as clinicians are not allowed to manage ongoing treatment directly to verify compliance and adherence.

Current developments in digital communication technologies provide new opportunities for home-based settings, facilitating both treatment delivery and remote monitoring, with a positive impact on the compliance and sustainability of the entire rehabilitation program. In this framework, Action Observation Treatment (AOT) shows intriguing potential for home-based applications[164, 291] (see chapter 1).

Several studies successfully applied AOT to children with CP. Buccino *et al.*[292] enrolled 15 children with unilateral or bilateral CP, randomizing them into two groups: the experimental group observed video sequences showing actions involving the use of the hands, which they then performed; the control group carried out the same actions observing videos without motor content. Hand motor function improvement after treatment was greater in the experimental group than in controls. Using a similar protocol, *Sgandurra et al.*[293] provided further evidence on the efficacy of AOT in improving the daily activity of children with unilateral cerebral palsy (UCP), even without clear effects on action kinematics. The authors concluded that children exploit the mirror mechanism to represent the action goal rather than its kinematics. A recent randomized-controlled trial[161] investigated the clinical and brain activity fMRI changes induced by AOT in children with CP. In addition to confirming the clinical efficacy of AOT on hand motor function, this study showed that children treated with AOT had stronger activation in a parieto-premotor circuit for hand-object interaction, supporting the notion that AOT is able to shape sensory-motor brain circuits sub-serving the impaired function.

Despite the valuable body of evidence on the efficacy of AOT in children with CP, other studies[171] have not confirmed its effectiveness as an “add-on” rehabilitative treatment, supporting the need to conduct further investigations in order to better define the optimal framework in which AOT protocols might be applied.

Favoring the understanding of others, the mirror mechanism plays a crucial role in social interaction and joint actions[232]. In childhood, successful early interpersonal coordination with peers is predictive of a more favorable social development[294, 295]. One might wonder whether interactive home-based AOT, simultaneously involving two peers, might not benefit more from the motor resonance driven by the mirror mechanism during social interaction. This strategy would also ensure a high level of engagement, as children might look upon the rehabilitation program as an interactive game with a fellow peer.

Given these premises, our study tested the feasibility and efficacy of an AOT home-based platform promoting child-to-child interaction to improve hand motor function in children with UCP.

2. Methods

2.1 Research design: This study used a within-subject time-series design where participants were their own controls[296, 297]. It was approved by the Local Ethics Committee (Comitato Etico Area-Vasta Emilia-Nord) and carried out according to the Helsinki Declaration. Written informed consent was obtained from the parents of each child.

2.2 Subjects: Subjects were recruited in cooperation with the *Fight The Stroke* association. Inclusion criteria were: age 5-10, confirmed diagnosis of UCP, evidence of predominately unilateral brain lesion at MRI, upper-limb Modified Ashworth Scale (MAS) sum-score<2, IQ≥70. Exclusion criteria were: attention/sensory impairment, uncontrolled seizures, previous orthopedic surgery or botulinum toxin-A injection within 6 months prior to entering the study. Overall, 52 children were surveyed; 32 did not fulfill the inclusion criteria, while 20 were enrolled.

2.3 Assessments and evaluation schedule: Hand motor function was evaluated using Besta Scale[298], which was developed in 1985 to assess grasp quality (hand function on request) and spontaneous hand use (bilateral manipulation). Several studies have been performed to test the scale's validity and reliability[284, 299, 300]. Besta scale is made up of 3 domains that respectively assess grasp quality (Besta A), spontaneous hand recruitment in task-specific bilateral manipulation (Besta B), and bimanual use in activities of daily living (Besta C). Grasp assessment is performed in a standardized setting by asking the child to use the affected hand to pick up different-sized objects. Tasks relative to Besta B and Besta C scales are standardized, including bimanual tasks whose number and type vary according to age. The minimal detectable changes (MDC) obtained for each domain starting from the original article[298] are as follows: Besta A=0.60 Besta B=0.52 Besta C=0.67. Showing an intra-rater interclass coefficient (ICC) value of 0.927[298], Besta Scale offers an excellent intra-rater level of reliability. To maintain comparability across children, Besta scores were expressed as a percentage of the maximum possible value of each domain. To measure global hand performance, we also calculated a Besta global score (Besta GS) as the area of the triangle centered on (0,0) having as vertices the values of Besta A, B, and C along three main directions.

In addition, we also evaluated upper-limb neurological motor impairment using the Fugl-Meyer upper extremity motor scale (FMA-UE)[301]. As part of general Fugl-Meyer Assessment (FMA)[301], FMA-UE has been adopted in several studies - both in adult stroke patients[302] and in hemiparetic children[303] - to assess treatment efficacy on upper-limb motor function. Test-retest reliability of FMA-UE (ICC=0.997[304]) shows an excellent profile, making this outcome measurement suitable for within-subject time-series design studies.

We tested upper-limb spasticity with the Modified Ashworth Scale (MAS)[305] together with upper-limb muscle segmental strength (MRC)[306]. Two subjective measurements were made: the 0-5 mood visuo-analog scale (VAS) and the caregiver subjective global impression of change (GIC). The former is a 5-point visual analog scale ranging from *"very sad"* to *"very happy"*, in which each point corresponds to a stylized facial expression (children were asked to tick the most appropriate face showing their mood). The latter was carried out by getting caregivers to answer the question *"How do you perceive the change in hand motor skills of your son/daughter that occurred in the last month?"* by ticking the most appropriate point on a graduation scale as follows: "markedly worsened"[-2], "slightly worsened" [-1], "unchanged" [0], "slightly improved" [+1], "markedly improved" [+2].

The above-mentioned measures were recorded one month before the beginning of the intervention (T-1), at baseline (T0, *i.e.* the beginning of home-based intervention), and at the end of treatment (T1). As additional baseline measures, we also collected NIH Stroke Scale (NIHSS), Total IQ (IQT), the Manual Ability Classification System (MACS)[307], Hand manipulative pattern classification (HC) according to Ferrari *et al.*[283], and ongoing pharmacological treatment.

2.4 **Outcome**: Primary outcome was the T1-T0 variation of Besta Scale global score. The secondary outcome was the T1-T0 variations of all the other tested variables (FMA-UE, MAS, MRC, VAS, GIC).

2.5 Experimental sessions: Each child underwent AOT sessions for 4 weeks (5 consecutive days/week, total = 20 sessions). Sessions were structured as follows: children first had to observe a 5′ pre-recorded video clip showing a wizard performing specific dexterity-demanding magic tricks. The wizard then instructed the children to internally reproduce the movement they had just seen, *i.e.* perform motor imagery. Thirdly, using a specific kit, the children had to imitate the wizard by carrying out the same upper-limb movements while receiving real-time feedback on the monitor. Positive, attractive feedback (*e.g.* sounds or light trails) took place only when a child moved a paretic limb, its movement being detected by means of a Kinect 3D camera. Finally, a child-to-child interactive session took place, with two children interacting via video connection while repeating the same exercises (see the video at the link https://vimeo.com/569342692). Children had already been matched with their peers during the enrollment phase, with age difference (max 24 months) as a main matching factor. Despite the primary outcome having age-standardized values, the matching aimed to facilitate social interaction during the daily peer-to-peer sessions. New tricks with increasing levels of difficulty were proposed weekly by the wizard, aiming to improve various manual skills (*e.g.* grasping, pronation and supination, fine hand dexterity). The exercises, aiming to progressively increase the demand for hand skills, were designed by a team of expert physicians specialized in neurorehabilitation, neurophysiologists, developmental psychologists, biomedical engineers, and therapists. All video sessions were remotely monitored and recorded and subsequently inspected by a neurologist. For non-adequate compliance with planned procedures, telephone contact took place to ensure the proper execution of the sessions. To enhance treatment fidelity, parents received a diary to record session details, together with reward stickers for the children to apply to the diary at the end of each week. Ongoing symptomatic treatment and physical therapy protocols targeting upper limbs were unmodified throughout the study.

2.6 Statistical analysis

This is the first study to use Besta Scale as a primary outcome to assess the effectiveness of AOT in improving hand function, hence the absence of previous data upon which to base a power calculation to estimate sample size. Thus, we first screened the largest possible population (n=52) of children with UCP and then enrolled only those satisfying the inclusion criteria (n=20).

Statistical analyses were performed using IBM SPSS version 25.0 for macOs. Non-parametric tests were used to evaluate changes across evaluation timepoints of ordinal outcome measures (Besta Scale, FMA-UE, MAS, MRC, VAS, GIC). A repeated-measures analysis of variance by ranks (Friedman test) was carried out to investigate the presence of a significant effect of time (T-1, T0, T1) on the following endpoints: Besta domains (Besta A, Besta B, Besta C, Besta GS), FMA-UE items (Upper Extremity, Wrist, Hand, Coordination-Speed), MRC, MAS, and VAS. Post-hoc comparisons were made using the Wilcoxon test and Bonferroni correction. Since GIC evaluation took place in only two time points (T0, T1), we directly performed the Wilcoxon test to evaluate this outcome.

Children that presented greater T1-T0 improvement in Besta GS compared to T-1-T0 were defined as responders. Subsequently, the correlation between the baseline clinical-demographical features and the primary outcome was evaluated using Spearman (ranked) correlation methods. The significance threshold was set at 5%.

3. Results

3.1 Demographical and clinical baseline data

The mean age of the 20 enrolled subjects (14 males) was 6.56±1.62 years. Overall, they presented mild-to-moderate hemiparesis with a mild level of spasticity, prevalent upper-limb involvement associated to significant hand motor deficit. The demographic, clinical, and neuroradiological features of each participant are shown in supplementary table 1.

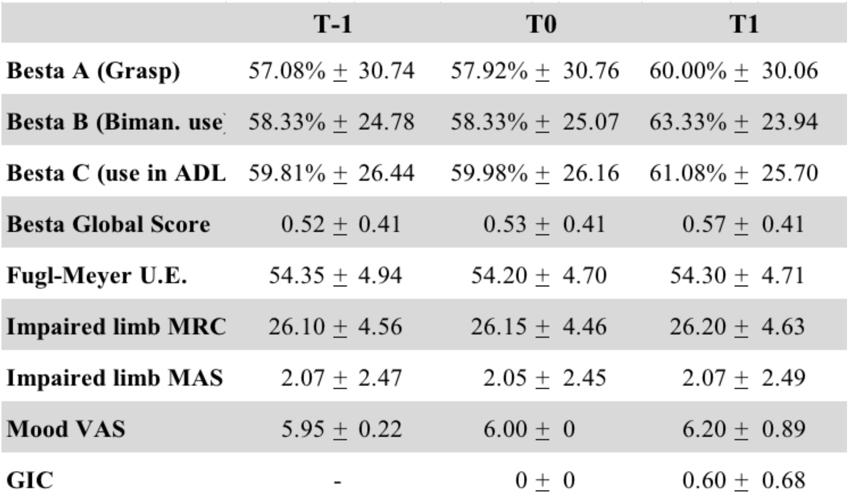
3.2 Outcomes results

Friedman test performed on Besta domains indicated a significant time-dependent difference in grasp abilities (Besta A, $\chi^2(2)=10.40$, $p<0.01$), in the recruitment of the paretic hand in bimanual tasks (Besta B, $\chi^2(2)=11.73$, $p<0.01$) and global hand motor performance (Besta GS, $\chi^2(2)=17.29$, $p<0.01$). A trend towards significance for inclusion of the paretic hand in activities of daily living was also observed (Besta C ($\chi^2(2)=5.15$, $p=0.076$).

Post-hoc comparisons (Figure 1) showed a significant T1-T0 difference for Besta GS (0.53%±0.41% *vs.* 0.57%±0.41, p=0.009). At the single scale level, significant T1-T0 improvement was found for Besta B score (58.33%±25.07 *vs* 63.33%±23.94, p=0.012). On the basis of Besta scale results, the total number of responders was 10 (response rate of 50%, mean percentage improvement of Besta GS 26.5%±21). Each absolute score change resulted greater than the Minimal Detectable Change.

Similarly, the subjective caregiver-reported impression of change showed significant improvement between T0 and T1 (0 *vs* 0.60±0.68, p<0.05). Subjective responders were 10 (50% of participants). No significant T1-T0 changes were found for FMA-UE, MAS, MRC, and VAS. Outcome values in T-1, T0, T1 evaluation time-points are shown in table 1.

Table 1. *Outcomes values across T-1, T0, T1 evaluation time points.*



	T-1	T0	T1
Besta A (Grasp)	57.08% ± 30.74	57.92% ± 30.76	60.00% ± 30.06
Besta B (Biman. use	58.33% ± 24.78	58.33% ± 25.07	63.33% ± 23.94
Besta C (use in ADL	59.81% ± 26.44	59.98% ± 26.16	61.08% ± 25.70
Besta Global Score	0.52 ± 0.41	0.53 ± 0.41	0.57 ± 0.41
Fugl-Meyer U.E.	54.35 ± 4.94	54.20 ± 4.70	54.30 ± 4.71
Impaired limb MRC	26.10 ± 4.56	26.15 ± 4.46	26.20 ± 4.63
Impaired limb MAS	2.07 ± 2.47	2.05 ± 2.45	2.07 ± 2.49
Mood VAS	5.95 ± 0.22	6.00 ± 0	6.20 ± 0.89
GIC	-	0 ± 0	0.60 ± 0.68

3.3 Correlational analysis

As the intervention was predominantly interactive, it is possible that the differences between a child and a peer in terms of either age or motor skills did influence the outcome. For this reason, we carried out correlational analysis, testing the link between the primary outcome on one side and 5 different measurements on the other, *i.e.* own age, own hand function at T0, age difference relative to the peer, the difference in hand function at T0 relative to the peer, and individual amount of daily practice.

Results showed significant correlation with the difference in hand motor skills relative to the peer (r=-0.519, p=0.019). In other words, the better the peer, the better the treatment outcome (Figure 2).

Figure 1.
Besta score variations across T-1, T0, T1 evaluation time points. Bars indicate s.e. of mean.

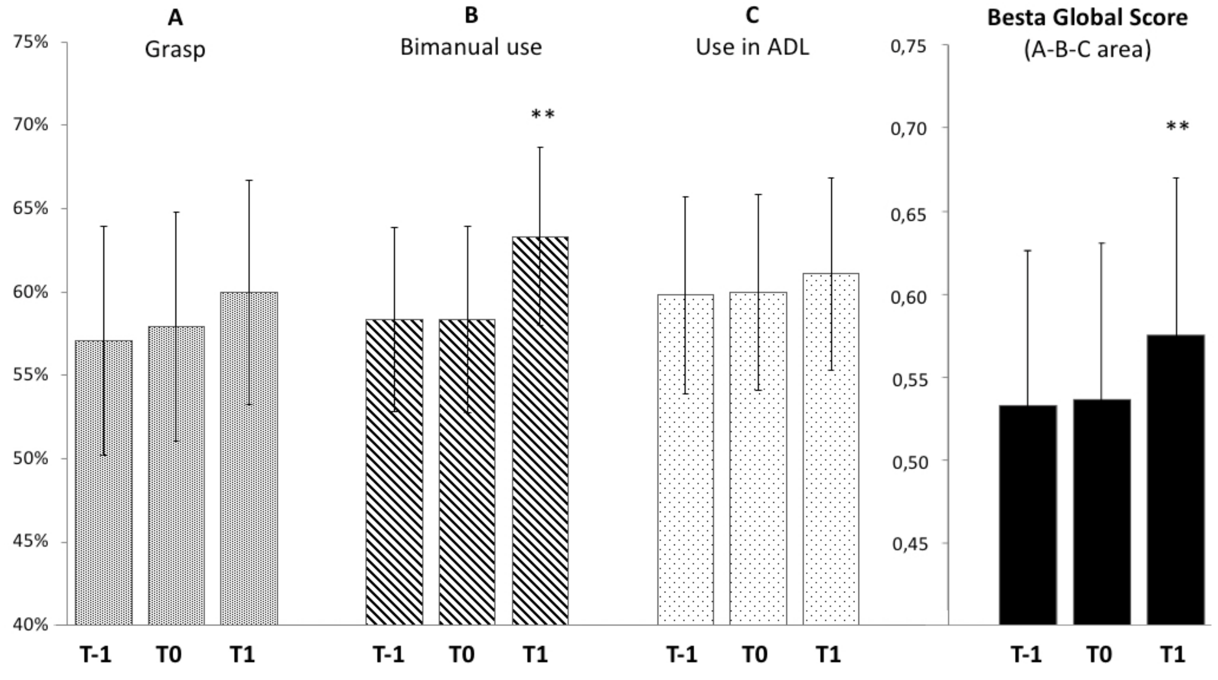
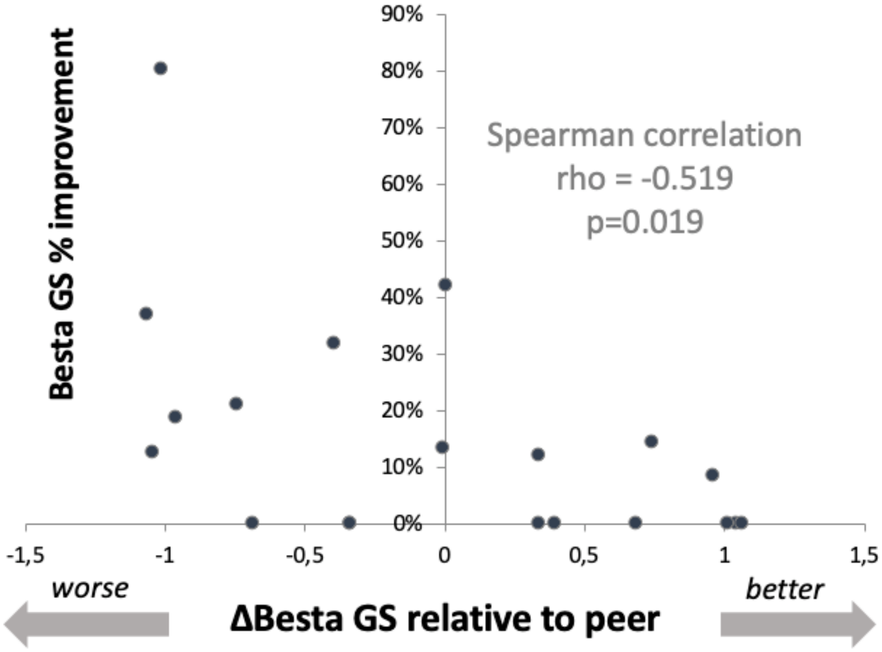


Figure 2.
Correlation between difference relative to peer in basal Besta and percentage T0-T1 Besta improvement. X-axis represents the baseline child-to-child difference in Besta Global Score. Negative values refer to children worse than their peers, positive values refer to those better than their peers. Y-axis represents the within-subject percentage improvement (T0-T1) in Besta Global Score. The inset text reports the coefficient and the p value of a Spearman correlation between X and Y values.



3.4 Compliance and safety

Compliance and adherence were optimal throughout; each of the scheduled sessions was completed without any drop-out. The mean amount of session practice at home for individual and child-to-child sessions was respectively 10′31′±28″ and 15′59″±6′22″. Control correlation analysis (Spearman rank test) was carried out between the amount of practice and the primary outcome. Only peer-to-peer practice was considered, as individual practice duration showed little variability. No significant correlation was found (R=0.267, p=0.256), ruling out the fact that primary outcome differences were related to different training exposure. Telephone contact was necessary only on one occasion for minor issues. Twenty therapy diaries (100%) were properly filled out and returned. No adverse events were observed.

4. Discussion

4.1 Outcomes

Our work studied the effects of a home-based AOT platform promoting child-to-child interaction on hand function, upper-limb motor impairment, spasticity, and caregiver-reported changes in a population of 20 hemiparetic children with UCP. Our results, supporting the evidence that AOT is able to improve hand motor function in UCP, are consistent with previous studies[292, 293, 308]. The observed improvement in hand motor performance is mainly due to the ability of children to use the affected limb in bimanual tasks, and, to a minor extent, to better grasping skills, in accordance with previous findings[293].

Score changes of participants who demonstrated improvement were greater than the minimal detectable change (MDC). This finding empowers the clinical reliability of our results; it is unlikely that outcome measurements are attributable to measurement errors. Whether the observed changes indicate a clinically meaningful difference (CMD) is more complex, since CMD has not been systematically investigated for Besta Scale. However, as suggested for scales such as Assisting Hand Assessment (AHA)[309], even small changes can be very meaningful for a child, should they imply functional gain. For example, the acquisition of the bimanual ability to drink from a cup using the impaired limb in cooperation with the contralateral one in a holding pattern in a child previously unable to recruit it for this aim, corresponding to 1 point gain in Besta Scale bimanual domain [298], might positively affect the child's independence in activities of daily living, and improve the quality of life.

Children with UCP often experience impaired bimanual coordination that affects their quality of life[310, 311]; lack of motivation, as well as motor impairment, is a key determinant in the tendency to avoid bimanual tasks[312]. Indeed, they often experience frustration when attempting to perform everyday two-handed tasks, and display greater negative reactions to failure than their healthy peers[313]. In order to enhance motivation and increase self-confidence, engaging themes (*e.g.* learning magic tricks) are often adopted in upper-limb interventions[314].

The goal-oriented tasks proposed in our study required constant bimanual coordination, yet were achievable by all participants, regardless of their hand manipulative pattern. Such a flexible approach to movement, together with the attractive feedback received after recruitment of the affected limb, might have encouraged children to use the paretic arm during execution, ultimately promoting its motor improvement. In fact, video recordings of the interactive sessions showed that children tend to tune reciprocally to the action goal rather than to its kinematics. In other words, they often perform the same actions, although with different spatiotemporal kinematics, in line with the study by Sgandurra *et al.*[293].

No changes in the degree of neurological impairment (as measured by Fugl-Meyer Scale) were found after treatment. This result might be interpreted on the light of the sensitivity of Fugl-Meyer and Besta Scales to various aspects of the motor behavior, as well as the treatment carried out. Indeed, while Besta Scale tests aspects of motor organization and behavior (e.g. the involvement of paretic arm in day-to-day actions, or the strategy adopted for hand-object interactions), Fugl-Meyer scores depend mainly on the presence of pathological neuro-motor features (e.g. synergistic patterns, spasticity, uncoordinated movements) regardless of the overall achievement of the tasks at hand. Thus, the administration of a treatment pushing children to achieve the same goal as the observed action might have favored an increase at the Besta Score and not at the Fugl-Meyer.

The absence of variations in MAS is in contrast with previous studies that demonstrate a beneficial effect of AOT on spasticity in children with UCP[315]. Of note, the lower level of baseline spasticity presented by our sample could have impeded a significant window of improvement. Likewise, the "ceiling effect" might explain the absence of significant variations on muscle segmental strength measured by MRC score.

The failure of basal hand impairment to predict treatment outcome -in contrast with other studies, where poorer hand function was associated with better response to rehabilitation[316, 317] - could be due to various factors: on one hand, the mild-to-moderate degree of impairment might have narrowed the window of improvement; on the other hand, the small sample size might have impeded the detection of a significant effect of this regressor on functional outcome.

Subject and caregiver compliance to intervention were very satisfactory: each scheduled session was completed without drop-out. Conducting the sessions in a familiar environment possibly helped with the successful adherence to this home-based and user-friendly protocol. The safety aspects of the study showed an excellent profile, without the occurrence of side-effects or adverse events.

The main limitation of the present study is represented by the non-blindness of the outcome evaluator. The resulting detection bias may have been in part reduced by the adoption of Besta Scale as primary outcome due to its item objectivity and excellent intra-rater reliability[298]. Another limitation of the present study is the small number of children enrolled, which was, however, adequate to detect the statistically significant effect of treatment on primary outcome.

Larger, possibly randomized-controlled studies with a between-group design, blinded assessments are necessary to validate the procedure's effectiveness and to propose its adoption as additional standard rehabilitation in children with UCP. Increasing the number of patients might also help identify the features able to predict the responsiveness to the treatment, as well as the best combination of common rehabilitation treatments and AOT for children with cerebral palsy.

4.2 Novelties and future perspectives

To our knowledge, our AOT study is the first to introduce the online delivery of positive and rewarding feedback targeting recruitment of the paretic limb. The sounds and light trails associated with the movement of the impaired limb conferred to the paretic hand an attractive magic-themed look, encouraging children to use it. As confirmation, videos showed that most children spent wait-times evoking the light trails on the screen by voluntarily and repeatedly moving the affected hand. Along with practice, feedback delivery[76] and reward[318] are regarded as powerful variables affecting motor-skill learning. Indeed, the use of reward is known to have significant implications in stroke rehabilitation, where motor learning interventions struggle to produce long-term changes in behavior[319]. Furthermore, reward is able to boost motivation, fostering engagement in the whole rehabilitative process[320], ultimately resulting in a more favorable outcome.

Reward delivery may also have helped keep the children engaged throughout the session, ultimately facilitating compliance to treatment. The possibility to remotely video-monitor AOT sessions allowed us to verify compliance and adherence to treatment procedures, even in a difficult-to-verify home-based setting. Moreover, this approach paves the way to the remote and silent monitoring of a rehabilitative trajectory in children that complements the online clinical picture of the patients. Another feature favoring our approach over more "traditional" home-based procedures is the availability of standardized stimuli and sessions that may easily be recalled by both children and families alike. Tailoring the treatment for each individual patient, as well as its sustainability for caregivers, is thus maximized.

The most relevant novel element of our study is the introduction of child-to-child interaction, by which children can take an active role in AOT, simultaneously being both "recipient" and "leader" during motor learning processes. One aspect of this relationship – the child-to-child difference in hand motor ability – is associated to treatment outcome, suggesting that the chances of improvement will increase should a child observe a peer with superior motor skills to his own. Of note, the magnitude of this effect is considerable, with child-to-child differences in hand motor ability explaining about 25% of the primary outcome variance.

The theoretical basis of such a dyadic learning model was addressed by Vygotsky during the first decades of the last century. He stated that learning in children is "socially-driven by processes by which they interact with the intellectual life of those around them"[321].Children, under the guidance of more capable peers, can imitate a variety of actions going well beyond the limits of their initial skill level. The Zone of Proximal Development (ZPD), defined as "*the distance between the actual skill level and the level of potential development through the achievement of new skills in collaboration with more capable peers*", is regarded as the field in which learning by imitation could take place during childhood[321]. The correlation we found between the difference in hand motor skills relative to the peer and the outcome of treatment suggested that ZPD framework can be also applied to child-to-child AOT. The peer-to-peer approach we propose could be further developed in light of available technologies in digital communication, paving the way to the realization of a vast network of patients undergoing interactive AOT. According to this novel approach, each user could in turn improve his abilities by interacting with a peer with superior motor skills, or by acting as a trainer and interacting with a more impaired individual. Besides maximizing the sustainability of the rehabilitation program, this strategy would easily be testable on a large-scale in all neurological conditions where AOT has proven effective (*e.g.* stroke, Parkinson's disease, multiple sclerosis).

5. Conclusion

Our results provide promising preliminary evidence on the effectiveness of home-based AOT associated with child-to-child interaction to improve hand motor function in children with UCP. Peer-to-peer difference in hand motor ability is linked to improvement, suggesting that it is preferable for a child to observe a leading peer with superior motor skills to his own. In conclusion, our AOT platform underlines its potentially helpful role in hand rehabilitation programs for children with UCP, extending traditional AOT approaches to novel social-enriched scenarios by which children could simultaneously be both recipient and leader within the motor learning process.

Supplementary table 1.

Demographic data, clinical features and radiological findings of subjects.

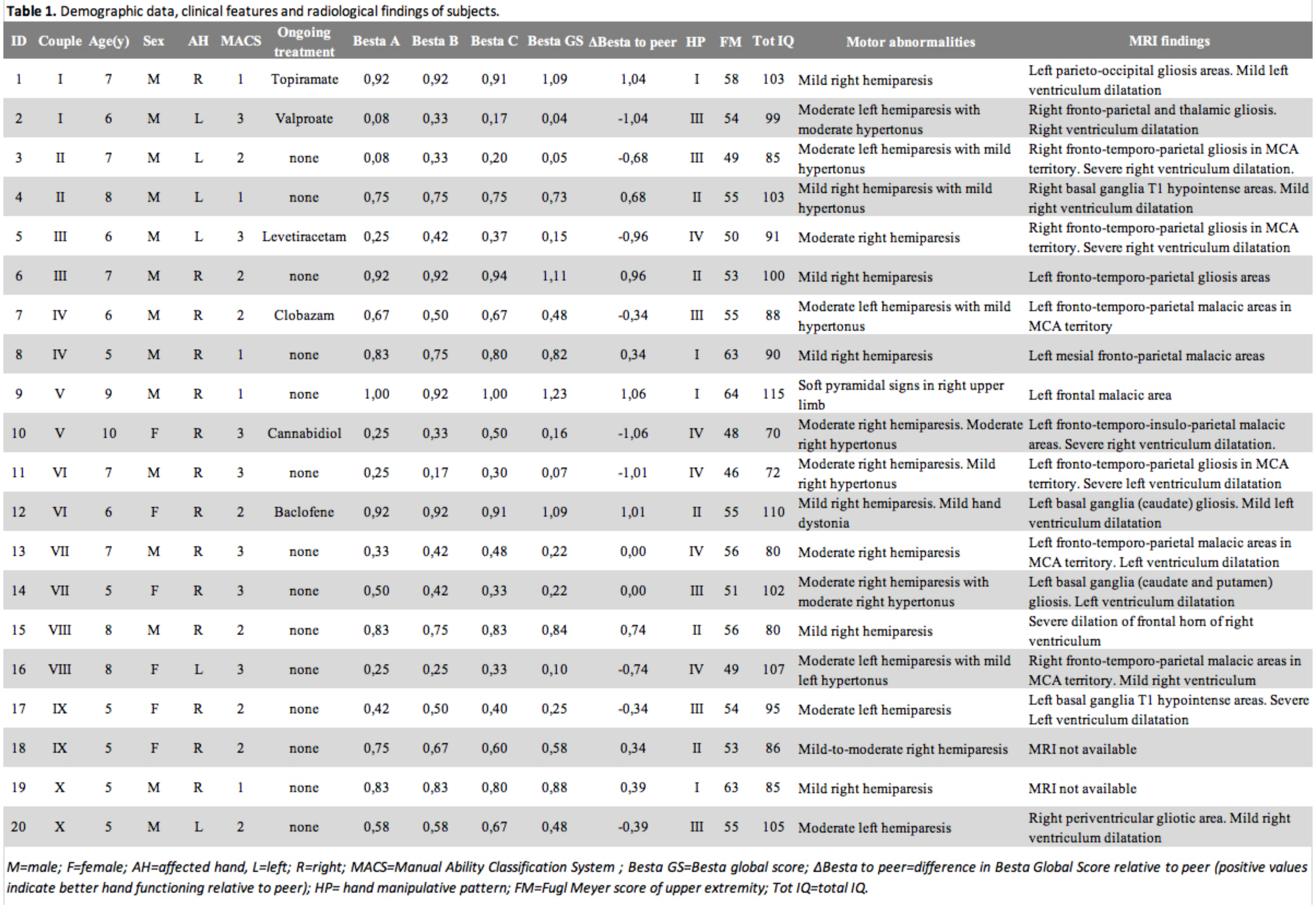


Table 1. Demographic data, clinical features and radiological findings of subjects.

ID	Couple	Age(y)	Sex	AH	MACS	Ongoing treatment	Besta A	Besta B	Besta C	Besta GS	ΔBesta to peer	HP	FM	Tot IQ	Motor abnormalities	MRI findings
1	I	7	M	R	1	Topiramate	0,92	0,92	0,91	1,09	1,04	I	58	103	Mild right hemiparesis	Left parieto-occipital gliosis areas. Mild left ventriculum dilatation
2	I	6	M	L	3	Valproate	0,08	0,33	0,17	0,04	-1,04	III	54	99	Moderate left hemiparesis with moderate hypertonus	Right fronto-parietal and thalamic gliosis. Right ventriculum dilatation
3	II	7	M	L	2	none	0,08	0,33	0,20	0,05	-0,68	III	49	85	Moderate left hemiparesis with mild hypertonus	Right fronto-temporo-parietal gliosis in MCA territory. Severe right ventriculum dilatation.
4	II	8	M	L	1	none	0,75	0,75	0,75	0,73	0,68	II	55	103	Mild right hemiparesis with mild hypertonus	Right basal ganglia T1 hypointense areas. Mild right ventriculum dilatation
5	III	6	M	L	3	Levetiracetam	0,25	0,42	0,37	0,15	-0,96	IV	50	91	Moderate right hemiparesis	Right fronto-temporo-parietal gliosis in MCA territory. Severe right ventriculum dilatation
6	III	7	M	R	2	none	0,92	0,92	0,94	1,11	0,96	II	53	100	Mild right hemiparesis	Left fronto-temporo-parietal gliosis areas
7	IV	6	M	R	2	Clobazam	0,67	0,50	0,67	0,48	-0,34	III	55	88	Moderate left hemiparesis with mild hypertonus	Left fronto-temporo-parietal malacic areas in MCA territory
8	IV	5	M	R	1	none	0,83	0,75	0,80	0,82	0,34	I	63	90	Mild right hemiparesis	Left mesial fronto-parietal malacic areas
9	V	9	M	R	1	none	1,00	0,92	1,00	1,23	1,06	I	64	115	Soft pyramidal signs in right upper limb	Left frontal malacic area
10	V	10	F	R	3	Cannabidiol	0,25	0,33	0,50	0,16	-1,06	IV	48	70	Moderate right hemiparesis. Moderate right hypertonus	Left fronto-temporo-insulo-parietal malacic areas. Severe right ventriculum dilatation.
11	VI	7	M	R	3	none	0,25	0,17	0,30	0,07	-1,01	IV	46	72	Moderate right hemiparesis. Mild right hypertonus	Left fronto-temporo-parietal gliosis in MCA territory. Severe left ventriculum dilatation
12	VI	6	F	R	2	Baclofene	0,92	0,92	0,91	1,09	1,01	II	55	110	Mild right hemiparesis. Mild hand dystonia	Left basal ganglia (caudate) gliosis. Mild left ventriculum dilatation
13	VII	7	M	R	3	none	0,33	0,42	0,48	0,22	0,00	IV	56	80	Moderate right hemiparesis	Left fronto-temporo-parietal malacic areas in MCA territory. Left ventriculum dilatation
14	VII	5	F	R	3	none	0,50	0,42	0,33	0,22	0,00	III	51	102	Moderate right hemiparesis with moderate right hypertonus	Left basal ganglia (caudate and putamen) gliosis. Left ventriculum dilatation
15	VIII	8	M	R	2	none	0,83	0,75	0,83	0,84	0,74	II	56	80	Mild right hemiparesis	Severe dilation of frontal horn of right ventriculum
16	VIII	8	F	L	3	none	0,25	0,25	0,33	0,10	-0,74	IV	49	107	Moderate left hemiparesis with mild left hypertonus	Right fronto-temporo-parietal malacic areas in MCA territory. Mild right ventriculum
17	IX	5	F	R	2	none	0,42	0,50	0,40	0,25	-0,34	III	54	95	Moderate left hemiparesis	Left basal ganglia T1 hypointense areas. Severe Left ventriculum dilatation
18	IX	5	F	R	2	none	0,75	0,67	0,60	0,58	0,34	II	53	86	Mild-to-moderate right hemiparesis	MRI not available
19	X	5	M	R	1	none	0,83	0,83	0,80	0,88	0,39	I	63	85	Mild right hemiparesis	MRI not available
20	X	5	M	L	2	none	0,58	0,58	0,67	0,48	-0,39	III	55	105	Moderate left hemiparesis	Right periventricular gliotic area. Mild right ventriculum dilatation

M=male; F=female; AH=affected hand, L=left; R=right; MACS=Manual Ability Classification System ; Besta GS=Besta global score; ΔBesta to peer=difference in Besta Global Score relative to peer (positive values indicate better hand functioning relative to peer); HP= hand manipulative pattern; FM=Fugl Meyer score of upper extremity; Tot IQ=total IQ.

Chapter 3

Body representation in children with unilateral cerebral palsy

This chapter is based on the article: *"Body representation in children with unilateral cerebral palsy"*. Nuara A., Papangelo P., Avanzini P., Fabbri-Destro M. Frontiers in Psychology, 2019 ;10:354

1. Introduction

Children have been using drawings to express themselves since ancient times[322]. The idea that spontaneous drawing of young children may reflect their physical, cognitive and affective status led psychologists to exploit drawings as a useful tool for assessing child development, personality and emotional adaptation[323–325].

One of the most used methods to measure the level of development through drawing is the DAM test (Draw-a-man)[324], which is a projective test using portraits: drawing a person, a child "projects himself in all of the body meaning and attitudes that have come to be represented"[326]. The body image, regarded as the conscious representation of the body parts and their relative position, involves both the subject's perceptual body experience with the body limits and conceptual understanding of the body in general[327]. Parallel to the body image is the so-called body schema, i.e. the subconscious ideas about the shape and size of the body and the relationship of the parts of the body to each other. While both these aspects affect the human figure drawing, deficits specific for body schema or body image are very difficult to separate[328]. For this reason, several studies refer to overall disorders of body representation to collectively describe these concepts[329].

Among neurological conditions, cerebral palsy (CP) is the one in which brain injury effects on body representation have been more extensively investigated by means of human figure drawing. Abercrombie and Tyson[330] used the DAM test in order to investigate body representation in CP, finding frequent anthropometric deviations and lacking body parts in a subset of drawings performed by hemiplegic children, probably reflecting children's projection of their own specific physical impairment. However, these observations were not translated in quantitative terms, nor authors required a self-portrait systematically.

The view that the representation of the 'self' in the generic DAM test is not firmly established[331] led some authors to prefer the self-portrait as an elective pictorial tool aimed to investigate children's self-body representation. Indeed, Morin and coworkers have shown that the self-portrait may give access to imaginary and symbolic aspects of subjectivity in normal subjects[332] and to the subjective effects of alterations in body image in patients with brain lesions[333, 334]. In this regard, Morin and colleagues[335] collected 161 portraits performed by hemiplegic stroke patients. Interestingly, these authors reported in a subset of right brain-injured patients a dissociation between self- and other-portraits: while drawing a "neglected" self-portrait, they spontaneously drew a complete image of others. These discrepancies persuaded the authors to embrace the idea that unilateral defects of portraits may selectively reflect the subjective alteration of the own body representation.

Asymmetrical self-portraits were not a constant feature in adult hemiplegic patients[335, 336]. This finding led authors to support a brain-damage onset-dependent hypothesis, postulating that that body representation (in particular its sensorimotor side, i.e., body schema) mostly forms in the early development[335, 337]. Thus, the relative timing between the stroke onset and the development of body schema/image could be a key determinant for the presence of asymmetrical features in self-portraits. In this regard, an ideal model is represented by perinatal stroke survivors, whose injury certainly precedes the body schema/image instantiation. Within such a population, it is possible to evaluate whether the motor impairment selectively impacts self-body representation rather than on body representation in general.

Enrolling a subpopulation of children with UCP involved in the study discussed in Chapter 2, we accounted for: (1) the influence of symbolic disturbances or neglect on self-portraying abilities, (2) the impact of motor impairment on the ability to perform a drawing, and (3) the "unawareness" of the impairment due to the hemiparesis onset posterior to body schema/image establishment processes. Using the test of the human figure, we asked children to draw a self-portrait, a portrait of a hemiparetic peer whom they joined in a child-to-child rehabilitation protocol, and a portrait of a healthy classmate. As controls, 18 age- and sex-matched typically developing children were asked to perform a self-portrait and a portrait of the best-classmate. We finally compared the drawings evaluating the asymmetry of representation of upper limbs, thus providing for the first time to our knowledge a quantitative index of self-portraits asymmetry.

In this study, we hypothesized that children with UCP present a larger asymmetry in self-portraits relative to other portraits and also relative to self-portraits of typically developing children. In addition, the direct comparison between self-portraits and the hemiplegic peer-portraits should reveal whether this asymmetry is specific for self-representation or vice versa whether it is associated to the "hemiplegic condition" representation.

2. Materials and methods

The study was approved by the Local Ethical Committee (Comitato Etico Area Vasta Emilia Nord) and was conducted according to the Helsinki Declaration. Subjects belonging to the clinical group were recruited in cooperation with "Fight The Stroke" association1, in the framework of a broader clinical rehabilitative protocol involving children with cerebral palsy. The families of the controls were enrolled in the realm of another study conducted in our Center on primary school children. Written informed consent was obtained from the parents of each child involved. Nineteen UCP children undergoing the child-to-child rehabilitative protocol described in the chapter 2 (clinical group) and 18 typically developing children (control group) were enrolled in the study. The rehabilitative protocol in which children with UCP were involved was composed of 30 daily sessions based on child-to-child interaction, with each participant interacting with another hemiparetic child, performing specific hand exercises. The interacting couples of children remained the same throughout the whole program, thus facilitating a social relationship between them.

Inclusion criteria of the clinical group were: age between 5 and 10; confirmed diagnosis of UCP; evidence of ischemic mono-hemispheric damage at brain MRI; Upper limb Modified Ashworth Scale (MAS) sum score < 2; Total IQ ≥ 70. Exclusion criteria were: attentive or sensory impairments; seizures not controlled by therapy; previous orthopedic surgery or botulinum toxin A injection in the upper limb within 6 months prior to study entry. Eighteen age- and sex-matched typically developing children were selected as controls. Evaluation of UCP and controls was conducted during a single session, in a clinical setting, according to the following procedures.

During the clinical evaluation, the following data were collected in children with UCP: neurological complete examination (verifying also the absence of body representation disorders in body-part pointing and naming, awareness of spatial notions and left-right orientation), Global hand motor skills using Besta Scale Global Score (Besta GS[298]), upper limb's spasticity by means of Modified Ashworth Scale (MAS)[305], hand manipulative pattern classification (HC) according to Ferrari et al[283] and total Intelligence Quotient (IQ) from WISC-IV battery[338]. Then, visuospatial constructional ability and visual memory were evaluated with Rey-Osterrieth Complex Figure Test (ROFC)[339] administered both in copy and early recall conditions (the latter performed 10' after figure visualization).

All children were asked to seat comfortably on a height-adjusted chair placed in front of a table and were provided with a set of pencils and white sheets. Children with UCP were asked to perform 3 drawings in the following order: a self-portrait (SP), a portrait of the best classmate-friend (FP), and a portrait of the hemiparetic child who joint them in the child-to-child rehabilitation program (HP). Controls were asked to perform a self-portrait and a portrait of the best classmate. To ensure a spontaneous body representation, no specific indication was given to children.

From the initial set of drawings, 9 triads performed by children with UCP and 2 dyads performed by controls were excluded due to the presence of non-anthropomorphic representations or non-measurable body parts. Drawings by 10 UCP children and 16 controls were finally considered for analyses. The length of each represented limb, measured as the inter-joint distance between the shoulder and the wrist, was measured. An asymmetry index (AI), consisting in the difference between the upper limbs length expressed as percentage of their average, was computed according to the following formula: $AI = \left|\frac{Left-Right}{Left+Right}\right| \times 2 \text{ x } 100$. Giving an example: if we consider a portrait with a left and right arm length, respectively of 5 and 4 cm, the AI = ∣ (5–4)/(5+4)∣ × 2 × 100 = 22.22%.

After verifying that the normality assumption was not met by AI data, a Kruskal Wallis H test was conducted to investigate between-groups differences in AI in portrait types. Within-group AI difference across portrait types has been investigated through a non-parametric repeated measures analysis of variance by ranks (Friedman test). Post hoc comparisons were conducted through non-parametric test (Wilcoxon), and effect size was computed by means of Eta squared and Kendall's W parameters for between- and within-group analyses. Subsequently, we tested whether asymmetry was correlated to age and/or to clinical variables indexing motor and cognitive functioning. By means of Spearman (ranked) test, the correlation between the AI and Age, IQ, Besta GS and HC were tested. This set of regressors was chosen to test whether age, intelligence level or motor functioning could impact on the AI. Significance threshold was set at 5%.

3. Results

The mean age of the 10 analyzed subjects with UCP (7 males, 3 females) was 7.06 ± 1.90 years. Overall, they presented mild hemiparesis with a mild level of spasticity (total MAS = 1.95 ± 1.34), a prevalent upper limb involvement associated to a significant hand motor deficit (Besta GS = 0.48 ± 0.38). According to the HC, 2 subjects belonged to type I ("integrated hand"), 2 to type II ("semi-functional hand"), 3 to type III ("synergic hand"), 3 to type IV ("imprisoned hand"). Visuo-spatial abilities evaluated with ROCF test showed values within ± 2 z-score for both copy and recall conditions (mean z-score = −0.09, range [−2, +1.65], mean z-score = −0.44, range [−1.92, + 0.91], respectively), according to the Italian pediatric normative[340] (see table 1 for individual ROCF z-scores collected in *copy* condition).

Neurological examinations show neither neglect nor hemiasomatognosia. All children were able to name their body parts correctly, no orientation abnormalities were detected, and spatial concepts were preserved. No children were excluded due their clinical profile. Overall, drawings were highly heterogeneous in terms of graphic style, with the precision and richness of details varying according to the age. However, an internal consistency was evident within-subject, with the three drawings presenting recurrent elements and a common graphical style (see Figure 1, panel A).

The control group was composed by 16 typically developing children (10 M, mean age 7.37 ± 1.75). As expected, ROCF test performed in controls returned normal values for both copy and recall conditions (mean z-score = 1.51, range [−0.5, 2.5] and mean z-score = 0.92, range [−0.86, 1.85], respectively).

The Kruskal-Wallis H test showed a statistically significant difference in AI in SP between two groups [$\chi 2(1) = 11.025$, $p = 0.001$, effect size: $\eta 2 = 0.418$]. Post hoc contrasts indicated a significantly greater AI in self-portraits by UCP children relative to Controls ($p < 0.001$, see Figure 1B).

Within UCP group, the Friedman test applied to the AI rendered a chi-square value of 11.4, returning a significant effect of portrait type ($p = 0.003$, effect size: Kendall's $W = 0.57$). In particular, children with UCP represented upper limbs more asymmetrically in self-portraits relative to other drawings (mean AI for SP: 39%, FP: 14%, HP: 22%). Post hoc contrasts indicated a significantly greater AI in self-portraits in comparison both to FP ($p = 0.005$) and HP ($p = 0.013$) (see Figure 1B). Moving to control group, no AI significant difference between SP and FP was found.

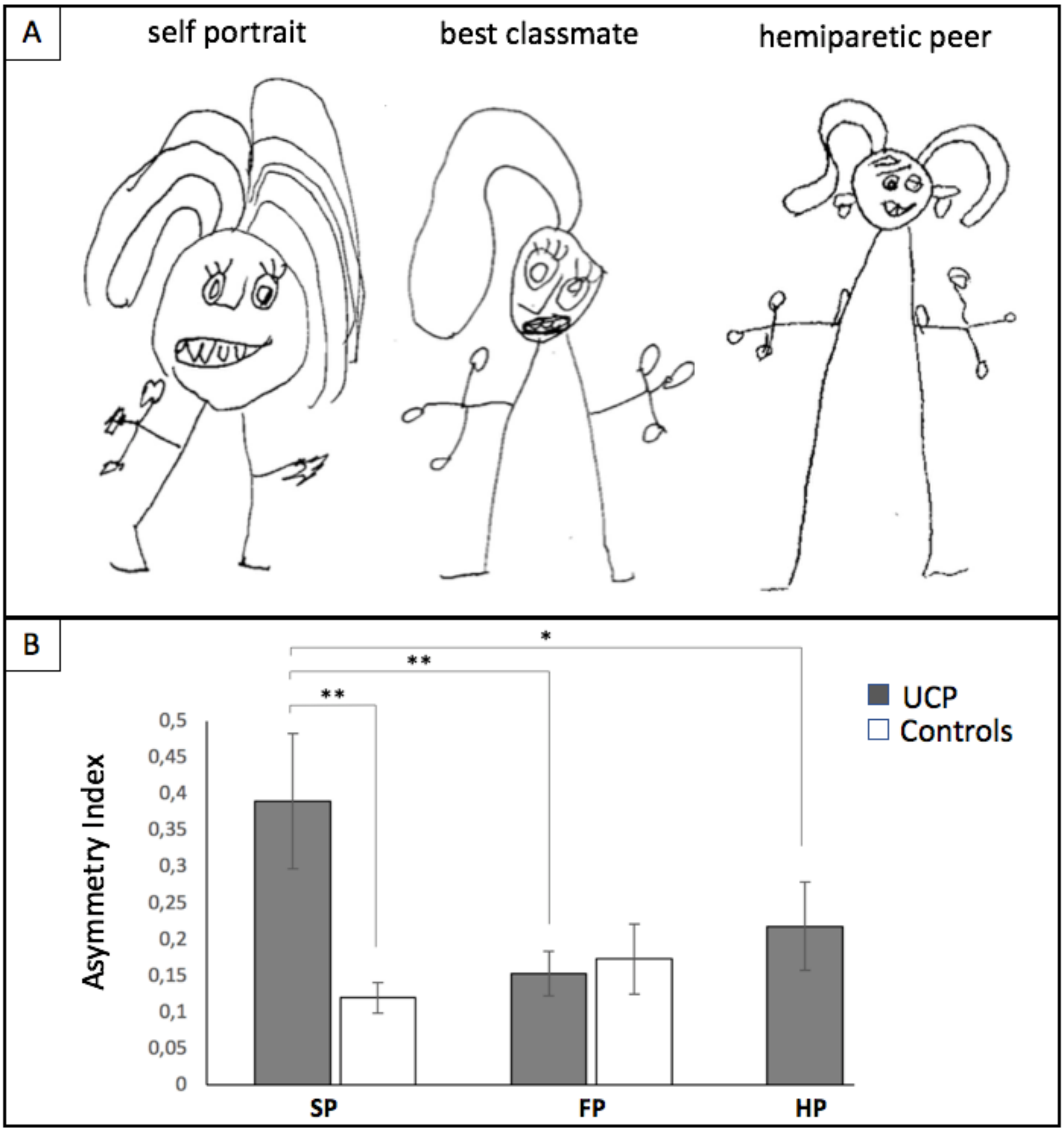
The study of clinical-demographical regressors on AI of self-portraits did not show any significant correlation. Besides, differential regressors related to the hemiparetic peer did not show significant correlations with the difference between SP and HP asymmetry indexes.

Table 1.: *Demographical data, clinical features and radiological findings of children with UCP.*

ID	Sex	Age(y)	AH	Total IQ	ROCF (z-score)	Besta GS	ΔBestaGS to peer	SP-AI	HP-AI	FP-AI	MRI findings
1	M	7	R	103	n.a.	1,09	1,04	0,36	0,20	0,29	Left parieto-occipital gliosis areas. Mild left ventriculum dilatation.
2	M	7	L	85	n.a.	0,05	-0,68	1,07	0,71	0,13	Right fronto-temporo-parietal gliosis in MCA territory. Severe right ventriculum dilatation. Corpus callosum hypotrophy.
3	M	8	L	103	1,65	0,73	0,68	0,10	0,11	0,07	Right basal ganglia T1 hypointense areas. Mild right ventriculum dilatation.
4	F	10	R	70	-2	0,16	-1,06	0,45	0,34	0,25	Left fronto-temporo-insulo-parietal malacic areas. Severe right ventriculum dilatation. Corpus callosum hypotrophy.
5	M	7	R	80	-0,2	0,22	0,00	0,67	0,04	0,15	Left fronto-temporo-parietal malacic areas in MCA territory. Left ventriculum dilatation.
6	M	8	R	80	-1,85	0,84	0,74	0,19	0,15	0,06	Severe dilation of frontal horn of right ventriculum.
7	F	8	L	107	0,15	0,10	-0,74	0,15	0,13	0,11	Right fronto-temporo-insulo-parietal malacic areas in MCA territory. Mild right ventriculum dilatation.
8	F	5	R	95	1,5	0,25	-0,34	0,20	0,21	0,04	Left basal ganglia T1 hypointense areas. Severe Left ventriculum dilatation
9	M	5	R	100	-1	0,88	0,39	0,45	0,08	0,10	n.a.
10	M	5	L	105	1	0,48	-0,39	0,26	0,20	0,17	Right periventricular gliotic area. Mild right ventriculum dilatation.

M=male; F=female; AH=affected hand; ROCF= Rey-Ostereith Complex Figure Test; Besta GS=Besta global score; ΔBestaGS to peer=difference in Besta Global Score relative to peer (positive values indicate better hand functioning relative to peer); SP-AI=self portrait asymmetry index; HP-AI= hemiparetic portrait asymmetry index; FP-AI=healthy classmate portrait asymmetry index; n.a.= not available.

Figure 1. ***Panel A***: *portraits performed by a subject: self-portrait, portrait of the hemiparetic peer with similar clinical conditions (5 years-old, unilateral cerebral palsy with prominent upper-limb motor impairment), portrait of her best classmate. Note - only in self-portrait - the asymmetrical representation of upper-limb, with the paretic hand smaller than the contralateral one and without fingers.*
Panel B: *Asymmetry index differences across different portrait types (SP, HP, FP) in Children with UCP and controls. Bars indicate s.e. of mean. *p<0.05, **=p<0.01.*



4. Discussion

The aim of the present study was to evaluate self-body representation in hemiparetic children affected by UCP with predominant upper limb involvement and to compare this pictorial representation to portraits of both hemiparetic and healthy peers. For this purpose, we evaluated the upper limb asymmetry in the three portrait types, which resulted significantly higher in self-portraits compared to both hemiparetic and healthy peers ones. Of note, self-portraits produced by typically developing children showed no significant difference in asymmetry, neither in comparison to portraits of others performed by the same group, nor relative to the portraits of others performed by children with UCP. This finding led us to regard the asymmetry of upper limbs in self-portraits as a specific signature of hemiparetic children.

The finding of asymmetries in own upper-limb representation in children with UCP is coherent with a previous work conducted by Abercrombie and Tyson[330] on children suffering from cerebral palsy, in which the occurrence of unbalanced representations of upper limbs were reported in children with an unilateral brain damage. However, these authors used the Draw-a-Man test[324] as a projective test, implicitly making children represent their own body image. Differently from these authors, we explicitly asked children to produce both self- and classmate- portraits. The possibility to directly compare these drawings allowed us to verify whether upper limb asymmetry reflects an alteration of the own body image rather than a deviant representation of human body in general. Two are the major strengths of this approach. On one side, the within-subject comparison allowed us to rule out the contribution of subject peculiarities in drawing. On the other side, despite diagnosed for UCP, our clinical sample was free from visuospatial and symbolic disturbances, hemiasomatognosia and neglect, thus controlled for major disorders affecting pictorial representation.

The finding of a three-times higher level of asymmetry in self vs classmate representation is in line with a previous work of Morin and colleagues[335]. These authors conducted a multivariate analysis evaluating 161 portraits performed by adult stroke patients (including both self-portraits and portraits of others). As expected, authors reported frequent “unilateral lacks” in right brain injured patients’ drawings, attributing these difficulties to several aspects of hemineglect. However, some right-hemiparetic patients, despite drawing a “neglected” self-portrait, spontaneously drew a complete image of others, leading to postulate that unilateral defects of portraits may selectively reflect an alteration of body self-representation.

Although in line with our findings, whether this deviant representation constitutes a signature of the self-representation, or rather it is a more general representation of the hemiparetic condition, is still unclear. To address this issue, we required participants to portray also a hemiparetic peer with whom they had been experiencing a daily interaction in the previous month. This condition allowed us to demonstrate that the asymmetrical picturing of upper limbs constituted a signature of the self-representation, favoring the view that self-portrait features are grounded in a first-person, sensorimotor bodily experience.

No correlation was found between the asymmetry in upper limb representation and indices of motor functioning. However, the small sample size and the heterogeneity of the investigated population in terms of brain lesions require further studies to reveal a possible link between these two domains.

5. Conclusion

In conclusion, our data indicate that UCP with predominant upper limb deficit affects body self-representation, but not body-representation in general. We suggest that the upper limb asymmetry does not constitute a picturing of pathological condition, but rather it may reflect the experienced status of motor functioning, that is valid only for one's own. We propose that evaluating self-portrait in hemiparetic children undergoing pediatric neurorehabilitation programs and quantifying the asymmetry of the self-representation could provide a valuable index of self-perceived functioning. Such procedure, well-suited for pediatric age, would enrich the clinical picture of the patient by adding a psychometric information to clinical outcomes, enabling clinicians to collect information not easily obtainable in pediatric patients.

Chapter 4

Telerehabilitation in response to constrained physical distance: an ideal framework for action observation treatment.

This chapter is based on the article: *"Telerehabilitation in response to constrained physical distance: an opportunity to rethink neurorehabilitative routines"*. Nuara A., Fabbri-Destro M., Scalona E., Lenzi S.E., Rizzolatti G., Avanzini P. J Neurol. 2021 Jan 15:1–12.

1. Introduction

The amount of training and its reiteration over time are key factors driving a favorable outcome of neurorehabilitative treatments[341, 342]. However, keeping a proper dosage and the repetition sustained in the course of time is demanding for all actors of neurorehabilitation. On one side, healthcare providers must face overscheduling despite limited availability of equipped spaces and specialized professionals; on the other side, families have to re-organize their daily routines planning travels to rehab facilities, and thus covering high costs in terms of money and time of caregivers[343, 344]. A key challenge in neurorehabilitation practice is to ensure timely access to cure and its continuity, removing all hindering factors. Among them, *constrained physical distancing* is one of the most detrimental since it may affect most of the neurorehabilitative procedures, spanning from the clinician/patient contact to the joint attendance of treatment spaces.

In this perspective, we will examine how the constrained physical distancing affects the prosecution of traditional neurorehabilitation programs, hurdling the continuity of rehabilitative pathways. We will propose that *telerehabilitation* approaches based on remote AOT administration could represent a valuable solution to sustain neurorehabilitative continuity of cure by overcoming social isolation barriers. Previous findings indicated that telerehabilitation may have a positive impact on a range of primary and secondary neurological outcomes[341, 345, 346] despite the large heterogeneity of interventional parameters and protocol design[345].

In summary, constrained social distance as the one experienced during 2020 pandemic could be seen as an opportunity to rethink current neurorehabilitative routines, envisioning mixed procedures in which face-to-face sessions are integrated and combined with AOT-based telerehabilitation.

2. The impact of physical distancing constraints on neurorehabilitation

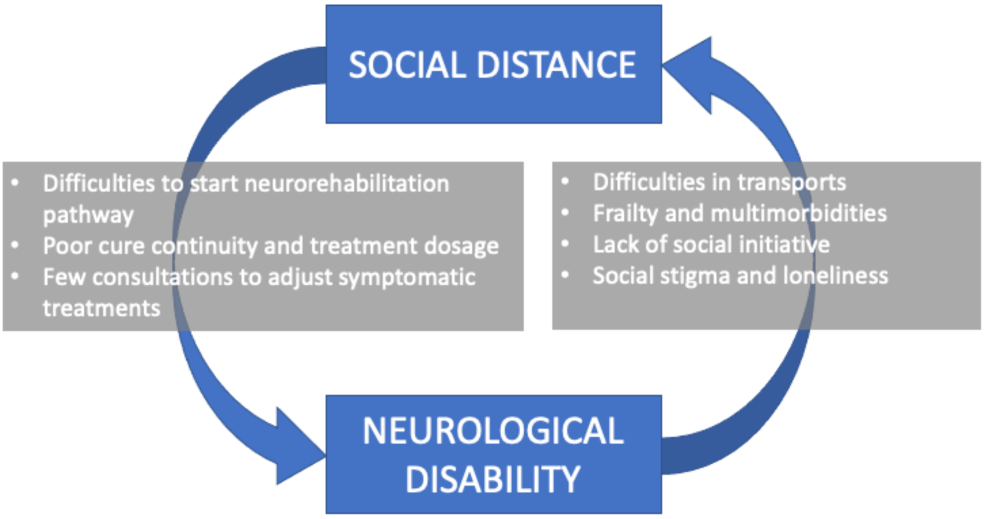
Neurorehabilitation is endowed with a peculiar social vocation. Indeed, its activities are grounded on the interaction across patients, caregivers and a multidisciplinary rehabilitative team, and usually take place in spaces hosting multiple patients who can potentially interact with each other. Therefore, physical distancing constraints severely affect common neurorehabilitative procedures. Exemplars are the consequences of the physical distancing measures combined with changes in healthcare services regulation following the recent Covid-19 pandemic outbreak, as also indicated by several national guidelines[347]. First, most of in-patients treatments have been confined to patient's room, which is intrinsically not conceived for hosting rehabilitation treatment; second, the clinical activities requiring an internal flow (e.g. movement between floors or to reach gym) have been suspended, as well as all the out-patients treatments or those delivered at home by therapists; third, meeting activities and clinical interviews with patient's familiars are currently conducted only by phone or email. Because of such radical measures, rehabilitation programs have been reduced, pursuing only short-term and primary goals, and the activities of the rehabilitative team have been limited to those strictly necessary. Noteworthy, beyond physical distancing measures, also changes in healthcare services access regulation are negatively affecting the access to rehabilitative services during the current pandemic.

Beyond pandemic condition, physical distancing constraints are daily experienced by immunocompromised individuals undergoing neurorehabilitation, e.g. people with aggressive forms of multiple sclerosis undergoing hematopoietic stem cell transplantation [348, 349], or frail neurological patients suffering from multimorbidity. Constrained distancing limits rehabilitative options also for patients with infectious disease requiring contact isolation[350]; also in these cases, the access to common spaces (e.g. gym, swimming pools) is restricted, and rehabilitative procedures are bounded to patient's room.

Outside the infectious prevention, physical distancing is a condition experienced also by people living in war zones, incarcerated[351], refugees[352], and, most widely, persons that live in remote areas of the world[353], especially in developing countries[354]. In such cases, the negative impact of distancing and isolation may be exacerbated by the difficulties in transports intrinsic to neurological disability[354].

The interplay between neurological disability and social isolation is worth a discussion. Indeed, disability by itself is an independent factor promoting social isolation for patients[355, 356] and caregivers[357]. Thus, all the physical distancing factors discussed above may favor the establishment of a vicious circle in which a poor continuity of cure, limiting the rehabilitative outcome, ends up in feeding physical distancing itself (see figure 1).

Figure 1.
The vicious circle involving social distance and neurological disability. Factors hurdling the continuity of rehabilitative pathways impede a favorable outcome, ending up in feeding social distancing itself



In this realm, adapting to physical distancing scenarios represents an imperative challenge for neurorehabilitation, whose settings and procedures need to be re-organized to guarantee the achievement of treatment objectives even in the absence of physical closeness among rehabilitation actors. Such solutions may spark the advantages far beyond the mere mitigation of pandemic effects, removing barriers that affect daily neurorehabilitative practice, and thus promoting its sustainability.

3. Telerehabilitation: an extra-weapon for physical distancing consequences

The recent advances in Information and Communication Technologies (ICTs) enabled a growing amount of people worldwide to remotely interact at affordable costs, embracing the possibility to join in complex human activities like neurorehabilitation. Telerehabilitation extends treatment delivery beyond the boundaries of traditional healthcare facilities, reaching patients regardless of the distance. This way, telerehabilitation would represent an extra weapon to contrast the detrimental impact of physical distancing on cure accessibility, offering advantages related to key factor of treatment outcome such as continuity of cure, maximization of treatment dosage, patient's motivation and availability.

Another point of strength of telerehabilitation relies on its home-based setting. Indeed, besides the logistic facilitations for patients and caregivers, the possibility to act in a familiar scenario may boost participation to procedures, especially in categories of subjects like children suffering from cerebral palsy[165, 171, 358] and cognitively impaired elder people[359], whose behavior and commitment to tasks may deteriorate when acting in unfamiliar environments[360].

Noteworthy, in order to be applied in a wide population and over prolonged times, treatments have to display an adequate sustainability. Telerehabilitation fulfills this requirement thanks to its capacity to relieve the care burden affecting caregivers and healthcare providers, impacting on the global economic cost by reducing travel expenses and decreasing loss of productivity time[361], in particular when applied to larger rural areas[362, 363].

All these factors may deeply contribute to establishing coherence between patient's behavior and prescribed indications, boosting a major factor of neurorehabilitation outcome, i.e. *compliance* to treatment. In this regard, a critical issue may be represented by the verification of patient's adherence to expected procedures. Even such a monitoring activity may be conducted via ICTs, using dedicated on-line daily questionnaires and diaries[165], as well as session video recordings acquired by means of webcams installed at patient's home[165, 358].

Aside to the above-mentioned strengths, telerehabilitation presents some weaknesses (see Peretti et al, 2017 [364]) such as the absence of in-person session monitoring and the heterogeneous evidence in terms of procedures, outcomes and effectiveness, narrowing a broader applicability.

Since advanced telerehabilitation is associated with an enhanced use of technologies as VR and sensors, it is worth to mention also the benefits and disadvantages specifically linked to their adoption. When dealing with technologically advanced procedures, a further limitation regards the low acceptance by people with poor confidence with digital technology. This issue, potentially involving both patients and providers, may be counteracted by a preliminary training and by implementing easily affordable procedures. Of note, scarce confidence with digital technology would likely reduce in the next decades, when *digital natives* will progressively represent an even larger slice of the overall population.

The main advantages and weaknesses of advanced telerehabilitation, as well as the measures aimed at counteracting limitations, are summarized in table 1.

Table 1.

Main advantages and limitations of technologically-advanced telerehabilitation.

	Advantages	Limitations	Countermeasures
Telerehabilitation	• Acting in a comfortable, home-based, setting • Possibility to reach remote locations • Dynamic adaptability to patient's profile and environment • Reduced transports • Increased sustainability of rehabilitative pathway	• Absence of in-person monitoring	• Adoption of technologically-advanced remote monitoring • Caregiver's active involvement and education
		• Absence of physical, face-to-face contact with healthcare personnel • Difficult symptomatic therapy adjustment • Difficult evaluation and management of spasticiy	• Adoption of a "mixed model", alternating traditional face-to-face neurorehabilitation with telerehabilitation
		• Heterogeneous evidences on telerehabilitative procedures, settings and outcomes.	• Adoption of standardized procedures and outcome measures • Systematic, research-oriented collection of data during telerehabilitation protocols
Use of technologically-advanced devices (e.g. Virtual Reality, sensors)	• Gamificated features boosting motivation and engagement • Creation of immersive or augmented virtual scenarios • Online feedback delivery • Acquisition of biomarkers via dedicated sensors • Administration in ecological, real-life environment • Patient's digital phenotyping	• Low acceptance by people with poor confidence with technology • Need of prompt technical assistance in case of malfunctioning • Side effects related to virtual reality (motion sickness syndrome) • Increase of equipment costs	• Preliminary patient's training • Implementation of easy-to-use, cost-affordable and safe equipment

4. A feasible telerehabilitative approach: Action Observation Treatment

Being grounded on the delivery of visual stimuli depicting actions to be trained, AOT is endowed with a special vocation for remote administration. Indeed, AOT has been recently opened to telerehabilitation, especially in pediatric population[164, 165, 358].

In chapter 3, a home-based, peer-to-peer AOT application for children with unilateral cerebral palsy has been discussed [165]. Here, during AOT remote sessions, participants had to observe and then imitate a wizard performing dexterity-demanding magic tricks. Kinematics were monitored via a markerless infrared system, and reinforcing feedbacks were provided upon the use of the impaired hand. Subsequently, a peer-to-peer live video-session to practice the same exercises took place. Following treatment, an improvement in hand motor abilities was found. Of note, peer-to-peer difference in hand motor ability was correlated to the amount of improvement, indicating that it is preferable for a child to observe a leading peer with higher motor skills. Beyond proving the feasibility of telerehabilitative approach for AOT, this study showed that in a "dual rehabilitation model", patients could simultaneously act as "beneficiaries" and "providers" within the motor rehabilitation process.

Scaling up the remote and peer-to-peer approach for dual rehabilitation, one could envision the realization of a wide network of patients undergoing interactive and remote AOT. Here, each user could in turn improve his skills by interacting with a more capable peer, or act as a trainer towards a more impaired individual. Beyond promoting a greater motor resonance [150, 165, 365], the interplay across patients experiencing the same symptoms would favour beneficial social instances, like reciprocal encouragement and other friendly exchanges. Besides the high sustainability, the peer-to-peer approach could be easily extended to other neurological conditions in which AOT has proven effective, opening technologically advanced telerehabilitation to novel, social-enriched frameworks.

As indicated for other task-oriented telerehabilitative approaches [18], remote AOT may potentially target various motor control features. Generally, tasks and exercises should meet the following criteria: (1) being challenging and meaningful, (2) addressing relevant and multiple impairments, (3) enhancing specific motor abilities through overload, (4) being endowed with goal-directedness in movement organization. A primary driver of task-specific self-confidence is represented by the successful performance accomplishment (see Winstein et al [366]). Associated gamification features and feedbacks delivery may emphasize this latter factor, ultimately boosting task-oriented effectiveness [367].

5. Suggestions for remote AOT implementation

As a general principle, the ideal telerehabilitative treatment should be intensive, warrant a proper repetition over time and sustain patient motivation and interest [341, 346]. Indeed, these are all factors contributing to maximize the neurorehabilitative treatment outcome.

The establishment of telerehabilitation in the daily routines of neurological patients necessarily implies the definition of key aspects impacting on its efficacy and sustainability. These include: a) the identification of patients eligible for receiving treatment, and the individualization of procedures, b) the definition of the setting, including devices and sensors collecting data relative to patient performance, and finally, c) the selection of signal processing procedures suitable to provide insights on the current patient performance, and possibly predict future developments. These points will be addressed separately in the next sections.

5.1 Patient eligibility and treatment individualization

With the exception of few procedures where physical contact between patients and therapists is essential, most of common neurological impairments may take advantage of remote AOT, whose procedures need to be tuned to patient's own impairments and rehabilitation objectives.

In the realm of stroke-related disability, upper-extremities motor training represents one of the most suitable scopes for telerehabilitation[341, 346]. Here, goal-oriented approaches have proven effective in inducing motor improvements similar to those produced by traditional in-clinic rehabilitation. Besides upper-limbs motor domain, also balance and gait symptoms due to stroke may benefit from telerehabilitative treatment [368]. However, the implementation of domiciliary setting for walking training is more challenging due to the limited space and to safety concerns. In this regard, the use of computer screens or projectors as viewing devices in place of immersive visors, and more generally the selection of wireless devices could prevent the risk of falls during training procedures [369].

The design of stroke telerehabilitative procedures should consider the presence of associated symptoms potentially affecting patient's adherence to treatment. Among them, spasticity – affecting about one third of patients with stroke[370]– might support the choice of customized and easy-to-handle haptic devices, as well as the adoption of sensors compatible with spastic hypertonia (e.g. sensorized gloves should be avoided). Moving to the visual domain, when symptoms like hemianopsia or unilateral spatial neglect concur, the design of stimuli and their administration need to be adapted to patient's own visual skills[371].

Among neurodegenerative movement disorders, Parkinson's disease (PD) is the one in which telerehabilitation is most adopted. In patients with PD, the remote delivery of motor tasks associated to visual, auditory or haptic feedbacks may be effective to improve postural stability and walking skills[372, 373]. Here, safety recommendations like those indicated above for gait training in stroke patients should be embraced. Interestingly, the potential application of telerehabilitation in PD goes beyond the training of gait-related abilities, encompassing the possibility to target upper limb motricity[374] or phonological skills[375]. Noteworthy, people with PD undergoing Levodopa pharmacological treatment should be instructed to perform training only during the ON state to limit the negative impact of motor fluctuation on telerehabilitative sessions [376].

Moving to younger subjects, telerehabilitation is facilitated by the higher degree of confidence with technology. This would be the case of people with MS. Consistently with the heterogeneous clinical manifestations of MS, here telerehabilitation can target multiple motor fields such as balance[377], gait[378], fatiguability[379], as well as cognitive skills like executive functions[380], verbal fluency and memory[381] (see also Di Tella et al. for a systematic review [382]).

Finally, in the realm of pediatric population, the remote administration of rehabilitative treatments may take advantage from the possibility to enrich sessions with gamificated features. This aspect – jointly with the instrinsic benefit of acting in a home-based setting – might be exploited in children with cerebral palsy, administering motivating task-oriented exercises able to improve upper limbs motor function[164, 165, 358].

Despite its encouraging potentialities, the administration of telerehabilitation may present relevant challenges in patients suffering from cognitive disturbances[359], where understanding of procedures may be impaired, and then adherence to treatment suboptimal.

Another instance where the adoption of telerehabilitation should be cautiously considered concerns patients with poor confidence or aversion toward technology. Such conditions - more frequent in elderly people - may be mitigated by a proper preliminary training, and by the choice of an easy-to-use setup.

Finally, patient eligibility must deal with neurological symptoms severity or possible comorbidities. For instance, verbal impairments impeding a proper communication with cure providers, as well as the occurrence of relevant cardiovascular comorbidities requiring continuous and supervised monitoring during active exercises could contraindicate the participation in telerehabilitation.

5.2 Remote AOT Settings

The ideal rehabilitation setting should combine the highest portability and smartness on the patient side, with the highest efficiency on the healthcare provider side. For simplicity, from here on, we will refer to these sides as patient- and therapist-, respectively.

The main elements composing the patient-setting are: a computer connected to internet, devices for audio-visual presentation, and wearable sensors interfacing with the computer for tracking the patient's performance.

Concerning hardware, current solutions maximize the portability and lightness of a tele-rehabilitative setup. Indeed, workstations with a Local Area Network (LAN) connection can be easily replaced to date by portable devices (laptops, tablets, or even smartphones) continuously connected to wireless networks. Although well-fitting with the notion of home-based telerehabilitation, such solutions would allow a full portability of the telerehabilitation setup, making patients capable to adhere to treatment at any time and any place.

While the above-mentioned devices allow the presentation of multimedia content, several rehabilitative practices adopted virtual reality (VR) to recreate realistic and three-dimensional environments in which patients may bodily operate. Among VR techniques, fully immersive VR is based on a completely computer-generated environment built to evoke the perception to be physically present in a virtual world. Here, the viewing medium is generally represented by a head-mounted visor. Conversely, in mixed reality (MR), real and virtual objects coexist, interacting in a mixed environment. Closer to the real-world scenario, augmented reality (AR) enhances the sensory experience of the real environment introducing computer-generated elements, encompassing the adoption of common devices like smartphones or tablets as viewing media. Noteworthy, the different degrees of immersion and physical interaction[383, 384] and viewing devices, need to be chosen according to patient’s specific features and rehabilitative aims.

VR technologies have been fruitfully applied to several neurological conditions, including stroke[385–388], Parkinson’s disease[376, 389], multiple sclerosis [377, 390] and cerebral palsy[391, 392], showing an overall satisfactory profile of feasibility and efficacy[393]. Modern VR-based systems (e.g. headsets integrated with haptic, auditory and visual feedbacks) allow the administration of a multi-modal, fully immersive stimulation, giving to the patient the vivid perception to be physically present in the virtual environment. Sometimes, VR users may experience symptoms of motion sickness (commonly referred as “VR sickness” or “cybersickness”), including dizziness, fatigue, disorientation and nausea. Several preventive measures have been proposed to mitigate such side effects, like providing multimodal stimulation, using dynamic adjustment of depth of field, increase the fidelity of virtual scenarios with synchronous and multimodal stimuli (see Chang et al [394] for a review). Novel all-in-one VR solutions merging the computer and the viewing device within a wireless headset, may include optical tracking systems and advanced visual adjustments to prevent the insurgence of dizziness and motion sickness, thus making VR technology applicable for a larger number of patients.

Beyond informing the patient, the ideal telerehabilitation setup should inform about the patient. Direct monitoring of patient performance is fundamental to verify the adherence to treatment, to ensure safety, and to monitor recovery trajectory. While the first two aspects can be fully achieved by means of teleconference systems, the recovery trajectory needs to be objectively quantified, estimating subtle changes in patient's performance by integrating specific monitoring devices in the rehabilitation system.

Portable mechatronic devices (i.e. haptic joysticks) represent one of the earlier and cost-effective solutions for upper-limb telerehabilitation. They can apply forces and measure hand position, thus indirectly quantifying the user performance[395]. However, these devices allow only few types of movement, hindering the possibility to evaluate fine motor actions like grasping or finger apposition[397]. To overcome these limitations, systems based on sensorized gloves have been developed and tested in neurological patients[391, 398]. Despite the promising results of their adoption in hand motor training protocols[391, 398], the potential dependence on caregivers for the wearing may represent a barrier for their use. Moreover, the exclusive monitoring of the hand does not permit the evaluation of concomitant postural attitudes of more proximal segments of the upper limb, as well as of the trunk[399]. In turn, Inertial Measurement Units (IMUs) systems are able to reconstruct accurately complex and multi-segmentary body postures also in outdoor environments. Nevertheless, these systems are often difficult to wear by neurological patients without assistance. The maximal independence of the patient could be ensured by optical marker-less solutions (e.g. portable infrared camera sensors), which however are mainly suited to track large movements[400]

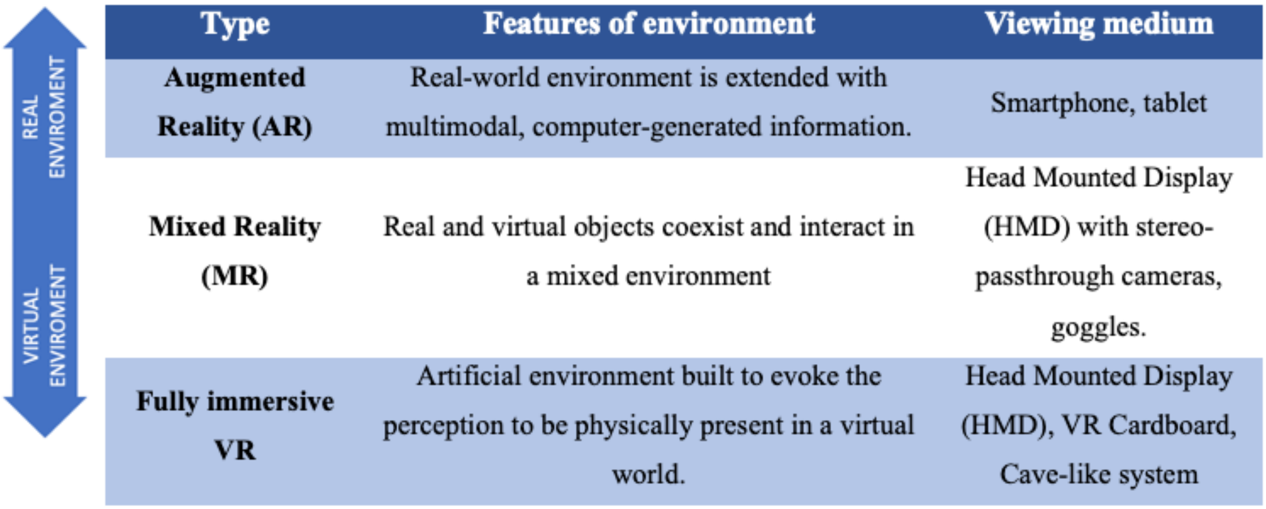
Concerning trunk and lower limbs kinematic evaluation, beyond IMUs, simpler wearable step counters (i.e. *podometers*) may provide information about gait parameters like walking speed, cadence, double support and stride with a reliability comparable to the gold standard for gait analysis[401, 402]. In addition, even smartphones can acquire useful objective data about gait and balance, being equipped with accelerometers and gyroscopes to detect body parameters such as falls, postural sway, gait performance, and balance stability[403, 404].

In summary, the choice of the appropriate sensor should be based on patient's neurological impairment, the primary outcome, the possibilities of assistance from the caregivers, and costs affordability. Moreover, to favor the detailing of patient's clinical picture, multiple and complementary types of sensors could be simultaneously adopted.

Once the patient-setting has been designed, an equally relevant part to take care of is the therapist-setting, i.e. the architecture enabling the home-based setup to download information relevant to the treatment delivery, and to upload data concerning the patient performance. Ideally, an online platform should be accessible 24/7 by both patients and clinicians, with secure accounts adhering to privacy international rules. The former can start a new session at their convenience, having stimuli and procedure automatically downloaded according to clinical prescription and to their own rehabilitative history. The latter, in turn, can access the system either to monitor online the patient performance (e.g. during the first home-based session or after relevant treatment change), or to review offline the same performance in light of the whole medical history.

Beyond facing security issues, the bidirectional data transfer between the patient- and therapist-settings should keep into account the possibility of connectional malfunctions, thus accounting for proper buffering and/or offline data storage strategies.

Table 2. *Basic features and administration modalities of the principal virtual reality technologies.*



Type	Features of environment	Viewing medium
Augmented Reality (AR)	Real-world environment is extended with multimodal, computer-generated information.	Smartphone, tablet
Mixed Reality (MR)	Real and virtual objects coexist and interact in a mixed environment	Head Mounted Display (HMD) with stereo-passthrough cameras, goggles.
Fully immersive VR	Artificial environment built to evoke the perception to be physically present in a virtual world.	Head Mounted Display (HMD), VR Cardboard, Cave-like system

5.3 Data processing

The use of sensors presents three main cascade advantages. The first is the *online* monitoring of patient's performance allowing clinicians and therapists to provide within-session feedbacks to patients or caregivers. Even if a simple webcam would be enough to detect large anomalies in behavioral performance of the patients, sensors could instantly signal subtle anomalies relative to previous history and/or to normative data.

A second advantage is the possibility to deliver online feedbacks aimed at encouraging appropriate patient's behavior[165] or - conversely - at discouraging unsuitable ones; in this regard, the adoption of strategies integrating sensors and virtual reality (e.g. the online visual amplification of patient's errors) may boost the learning process[383], biasing patient's behavior toward the correct one.

Finally, the therapist-platform can be embedded with signal processing tools capable to identify relevant features about individual patient performance and history, and to compare them against data from other patients matched for clinical conditions. In addition, to provide relevant insights on the long-term dynamics of patient's performance, this approach would pave the way to digital phenotyping[405], and the subsequent implementation of machine-learning models aimed to predict functional outcomes. Such information would ultimately support choices and adjustments by the clinicians, thus maximizing the beneficial effects of the whole rehabilitative pathway.

6. Conclusion

Thanks to modern technology, an exclusive telerehabilitation represents the only valuable and scalable solution in case of constrained and persistent social distance requirements, making patients act in virtual scenarios while remotely interacting with clinicians. In this field, due to its methodological peculiarities, AOT represent an elective approach.

The lesson taught by COVID-19 pandemic, however, could partially apply also to daily neurorehabilitation routines, so to relieve the care burden around neurological patients and their management. Indeed, while *face-to-face* therapeutic interactions represent an irreplaceable element in the relationship between patients and healthcare providers, telerehabilitative AOT sessions could act as the missing pieces of the puzzle leading to an optimal continuity of cure.

In such a "mixed" model of neurorehabilitative care, hospital-based procedures (e.g. post-acute protocols, clinical-neurophysiological evaluations, intensive training, etc.) might be used mainly to forge the scaffold of the rehabilitative program, while telerehabilitation could be prevalent in the long-term consolidation of functional progresses[406]. The development of this model requires the synergistic involvement of clinicians, therapists, engineers, developers along with caregivers and patients to promote the overall sustainability and effectiveness of the rehabilitative pathway.

Conclusion

The first systematic application of action observation treatment (AOT) dates from the early 2000s[407]; since then, AOT has been widely adopted in multiple clinical and not-clinical context[227]. However, despite the huge body of research on mirror mechanism in the last decades[228], limited findings on neural substrates of AOT efficacy are available, most of them investigating treatment's ongoing correlates [134, 146, 161, 174] rather than explaining its efficacy. Moreover, most of current AOT applications adopt traditional, not-ecological settings, where digital technology is underexploited. Given these premises, the present thesis added two relevant advances to AOT application.

First, the identification of electrophysiological signatures explaining AOT efficacy provided new insights on its underlying cortical mechanisms, envisioning the development of predictive assessments for the selection and identification of best candidates for AOT. Such knowledge would help clinicians improve the accuracy of prognoses and personalize rehabilitation plans and increase equity of access to rehabilitation services. It is worth noting that predictive tools use is not intended to hinder admittance to rehabilitation since patients can still meaningfully benefit from therapy even if they are expected to achieve only a partial outcome. In this view, predictive assessments would rather serve for tuning the rehabilitation planning and setting[408].

The second element of novelty is the inclusion of peer-to-peer interaction, so that "traditional" AOT may be extended toward novel socially enriched scenarios, where trainees might simultaneously be recipients and leaders within motor learning process. Beside exploiting for the first time the "social" side of *mirror mechanism* within AOT, peer-to-peer interaction represents a timely opportunity, considering the current facilitation of interpersonal connection offered by digital technologies. Actually — even if outside AOT conventional scopes — millions of stimuli depicting other's actions are exchanged every day worldwide [409], breaking down any physical barrier: now more than ever, action observation pervades our life. It might be a good time to learn from other's actions.

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