Translational effects of robot-mediated therapy in subacute stroke patients: an experimental evaluation of upper limb motor recovery

Eduardo Palermo¹, Darren Richard Hayes¹,², Emanuele Francesco Russo³, Rocco Salvatore Calabrò⁴, Alessandra Pacilli¹ and Serena Filoni³

¹ Department of Mechanical and Aerospace Engineering, Sapienza University of Rome, Rome, Italy
² Seidenberg School of Computer Science and Information Systems, Pace University, New York, NY, USA
³ Fondazione Centri di Riabilitazione Padre Pio Onlus, San Giovanni Rotondo, Italy
⁴ IRCCS Centro Neurolesi ‘Bonino-Pulejo’, Messina, Italy

ABSTRACT

Robot-mediated therapies enhance the recovery of post-stroke patients with motor deficits. Repetitive and repeatable exercises are essential for rehabilitation following brain damage or other disorders that impact the central nervous system, as plasticity permits to reorganize its neural structure, fostering motor relearning. Despite the fact that so many studies claim the validity of robot-mediated therapy in post-stroke patient rehabilitation, it is still difficult to assess to what extent its adoption improves the efficacy of traditional therapy in daily life, and also because most of the studies involved planar robots. In this paper, we report the effects of a 20-session-rehabilitation project involving the Armeo Power robot, an assistive exoskeleton to perform 3D upper limb movements, in addition to conventional rehabilitation therapy, on 10 subacute stroke survivors. Patients were evaluated through clinical scales and a kinematic assessment of the upper limbs, both pre- and post-treatment. A set of indices based on the patients’ 3D kinematic data, gathered from an optoelectronic system, was calculated. Statistical analysis showed a remarkable difference in most parameters between pre- and post-treatment. Significant correlations between the kinematic parameters and clinical scales were found. Our findings suggest that 3D robot-mediated rehabilitation, in addition to conventional therapy, could represent an effective means for the recovery of upper limb disability. Kinematic assessment may represent a valid tool for objectively evaluating the efficacy of the rehabilitation treatment.

INTRODUCTION

Stroke, both ischemic and hemorrhagic, affects about 10 million people every year worldwide (Vos et al., 2015), representing the second most frequent cause of death,
after coronary artery disease and is the leading cause of disability in the elderly (Wang et al., 2016). Many stroke survivors (about 42 million in 2015) (Vos et al., 2016) sustain neurological damage, which is often permanent. Among other impairments, stroke can compromise use of the upper limbs, thereby negatively impacting common daily living activities (ADL) (Papaleo et al., 2015).

Although stroke patients are usually able to recover their ability to walk independently in a relatively short time, thanks to advanced rehabilitation therapies, a complete recovery of upper limb function is not as common (Cho & Song, 2015). Hence, effective therapies must be repetitive, target-oriented, and intense, in order to stimulate the neural plasticity processes, and are fundamental to the recovery of motor functionality (Colombo et al., 2013). Traditional therapy, manually administered by rehabilitation operators, rarely meets all of these criteria. The introduction of assisted robot therapy has improved the efficacy of upper limb rehabilitation and significantly improved the living conditions of patients (Rahman et al., 2016).

In recent years, technological advances, and increasing interest in robotic rehabilitation, have led to the development of high performance machines that can provide support to the rehabilitation operator; in some cases, they can even perform a perfectly complementary job (Masiero et al., 2007). Since the 1990s, these devices have become more pervasive. The first models allowed the operator to utilize pre-set tasks, and were activated ‘as needed’ (Squeri, Basteris & Sanguineti, 2011), (Reinkensmeyer, 2003), thereby allowing the rehabilitation operator to follow multiple rehabilitation treatments simultaneously (Wisneski & Johnson, 2007). More recently, robots have integrated rehabilitation strategies that adapt to patient feedback. For example, robots can react to forces applied by the patient during rehabilitation (Kahn et al., 2006).

An essential feature of robotic devices is the ability to perform repetitive movements over a long period of time. The repetition and intensity of exercises are crucial in rehabilitative therapies for patients affected by stroke or other neurological pathologies. Research has shown that neural plasticity is preserved after a brain injury, thereby allowing for new connections to form between the neurons while their gradual reorganization can restore movement and functionality to the affected limb (Turner et al., 2013). Thanks to the virtual environments where exercises are performed, in the form of games with specific goals, the patient is more immersed compared to traditional therapies, which constitutes a further benefit.

Noteworthy, examples of upper limb rehabilitation robots currently available on the market or in research laboratories include the MIT-Manus for the end-effector typology (Hogan et al., 1992, 1993), and the Armeo® Power exoskeleton (Hocoma, Inc., Volketswil, Switzerland; https://www.hocoma.com/us/solutions/armeo-power/), which is derived from the research prototype Armin (Mihelj, Nef & Riener, 2006; Nef et al., 2006). The latter has been involved in studies that introduced a novel rehabilitation solution to foster neural plasticity, which showed promising results derived from transcranial magnetic stimulation (Calabrò et al., 2016).

Rehabilitation mediated by robots also provides quantitative results about improvements in task execution, thereby allowing researchers to quantitatively monitor
the recovery of limb functionality (Panarese et al., 2016). These performance indicators represent a fundamental method to evaluate the administration of specific rehabilitation protocols or the prescription of different exercises during rehabilitation. Performance data used to estimate the patient’s motion capabilities can be obtained during specific exercises, via software installed on the device.

Considering this potential, robot-mediated therapy (RMT) became prominent in research activities that were focused on improving traditional rehabilitation paradigms (Stein, 2004). Although many studies to date have reported on the recovery of post-stroke patients treated through RMT, it is still difficult to assess the extent to which these results go beyond traditional therapies administered within a comparable timeframe (Norouzi-Gheidari, Archambault & Fung, 2012). In other words, despite the greater level and quality of both support and stimulation provided to patient, and the evaluating tools made available to clinicians, demonstrating higher effectiveness in recovery of RMT with respect to traditional therapy is still an open challenge.

One reason for this lack of evidence lies in the heterogeneity of RMT solutions and, consequently, in the wide variety of strategies that have been proposed to evaluate its effects. To analyse pre-post treatment effects, many studies have combined a kinematic evaluation of patients’ motor performance compared to traditional evaluation techniques, in an effort to overcome the intrinsic challenges associated with replicating clinical scales (Prange et al., 2006). In fact, despite being designed to comprehensively evaluate different aspects of motor deficit resulting from a stroke, clinical scales are prone to uncommon sensitivity, ceiling effects, and subjectivity in their administration by the operator (McCrea, Eng & Hodgson, 2002; Rohrer et al., 2002; Bosecker et al., 2009). However, in most cases, this type of supplementary metric is calculated on the same gestures performed for the treatment. Consequently, in order to reveal the translational effects of rehabilitation, an evaluation of the motor performance regained by the patients should involve gestures that mirror daily activities, and are derived from the RMT scenario (Van Kordelaar, Van Wegen & Kwakkel, 2014).

Several studies have assessed the possibility of using a kinematic evaluation based on a simple daily-life inspired gesture, to objectively assess stroke-related motor impairment. Van Kordelaar, Van Wegen & Kwakkel (2014) proposed evaluating kinematic parameters that are based on the hand trajectory recorded by an electromagnetic motion tracking device, during a simple exercise based on reaching and moving objects on a table. A similar paradigm was proposed by Rohrer et al. (2002) that assessed motion smoothness changes during recovery in the aftermath of a stroke by leveraging a MIT-Manus. However, these movements are planar and the gravity load effect is supported by the robot or by the table. In contrast, a 3-DoF protocol would facilitate an evaluation of the final effect of recovery, where the force exerted for a vertical elevation of the hand plays an important role. Caimmi et al. (2007) proposed a 3-DoF protocol where the subject was tasked with reaching towards a target placed in front of him at shoulder level and starting from a lower position. Kinematic indices, based on motion capturing, demonstrated improvements for stroke survivors thanks to constraint-induced movement therapy (Caimmi et al., 2007).
In this paper, we adopted a protocol similar to the one introduced in Caimmi et al. (2007), for evaluating the translational effects of an RMT-based rehabilitation project and administrated to 10 stroke survivors, using a rehabilitation exoskeleton: the ARMEO Power device. In particular, we primarily sought to investigate whether kinematic indices, based on motion capturing a 3D daily-life inspired gesture, improved after the administration of an RMT protocol, which involved an exoskeleton for 3D upper limb rehabilitation. As a secondary goal, we evaluated how these indices are in agreement with patient assessments that have been assessed using the most widely adopted clinical scales for post-stroke motor impairment.

**METHODS**

**Patients’ description**

A total of 10 subjects (eight males and two females, mean age 60.1 ± 18.3 years) affected by stroke in the sub-acute phase (4.0 ± 1.5 months after the event; five with left and five with right hemiparesis) were enrolled in the study.

Inclusion criteria were:

- unilateral paresis from a single supratentorial stroke occurring at least six months prior;
- sufficient cognition to follow simple instructions and understand the purpose of the study (Mini-Mental State Examination score > 18 points) (Masiero et al., 2007);
- ability to perform the task proposed (pointing at a target, with the unaffected and with affected limb);
- ability to remain in a sitting posture.

Exclusion criteria were:

- participation in other studies or rehabilitation programmes;
- bilateral impairment;
- severe spasticity (Modified Ashworth Scale score ≥ 3);
- severe sensory deficits in the paretic upper limb;
- other neurological, neuromuscular or orthopedic (shoulder sub-luxation or pain in the upper limb) disorders, or visual deficit;
- refusal or inability to provide informed consent;
- other concurrent severe medical problems.

Table 1 reports the primary clinical data of the patients included in the study. Patients were clinically evaluated using the four most adopted rating scales in stroke: the motor sub-section of the Functional Independence Measure (FIM) (Liao et al., 2012), Barthel Index (BI) (Parker, Wade & Hewer, 1986), Frenchay Arm Test (FAT) (Heller et al., 1987), and Fugl-Meyer Assessment (FMA, Motor function sections, maximum score 66) (Sullivan et al., 2011).
Treatment protocol and device

This study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committees of IRCCS Centro neurolesi Bonino Pulejo (study registration number 43/2013). Informed consent was obtained from all subjects enrolled in this study.

Patients underwent a rehabilitation programme of 20 sessions, each lasting 50 min, five sessions per week, using the Armeo® Power exoskeleton, in addition to a session of conventional rehabilitation therapies conducted with the same duration.

The Armeo® Power (Fig. 1) is a motorized orthosis for the upper limb with six degrees of freedom (DoFs): three DoFs for the shoulder, one for the elbow flexion, one for the forearm supination, and one for the wrist flexion. Each joint is powered by a motor and equipped with two angle sensors.

The device can support the patient’s arm weight, thereby providing a feeling of fluctuation, and assists it in a large 3D workspace during execution of the exercises. The presence of a suspension system allows the facilitator to set and adjust the sensitivity of the robot depending on the characteristics of each patient. Arm and forearm lengths are both adjustable, so that the device can be adapted for use by a large selection of patients.

The interface used for the execution of exercises, which appear in the form of games, is designed to simulate arm gestures and provide a simple virtual environment. Increasing levels of difficulty can be selected, which in turn determines the speed of the movements, their direction and the work area, depending on the degree of motility of the subject undergoing rehabilitation.

Each robotic session, which lasted 50 min, consisted of: 10 min of passive mobilization for familiarization and to decrease the patient’s spasticity, if present; and 40 min of task-oriented exercises that were calibrated according to the patient’s abilities and with increasing difficulty over the course of the training period.

Experimental setup for kinematic analysis

To evaluate the effects of the prescribed treatment, patients underwent a 3D kinematic analysis, both pre- and post-treatment. Patient movements were recorded during a pointing task (Fig. 2), using an Optoelectronic System, the BTS SMART-DX 300
(BTS Bioengineering, Brooklyn, NY, USA; http://www.btsbioengineering.com), which consists of six infrared CCD cameras with a resolution of $650 \times 480$ pixels, and an acquisition rate of 120 Hz.

In this study, a subset of the kinematic model proposed by Rab, Petuskey & Bagley (2002) has been adopted, to ensure the optimal execution of the exercise. In particular, the head, neck, and pelvis segments have been removed. Reflective markers were placed on
the patient’s body, referenced in the model (Fig. 3). The wrist joint is modelled as a universal (saddle) joint with two DoFs, where wrist movement occurs in flexion-extension and radio-ulnar deviation; the elbow like a hinge joint with two DoFs; the shoulder as a spherical joint with three DoFs.

The pointing task designed for 3D kinematics acquisition required reaching a target, placed on the subject’s sagittal plane, at shoulder height, and at a distance from the body equal to the patient’s arm length (measured from the acromion marker to the midpoint between the radius and ulna markers). The patient was sitting on a chair with his hands stretched along his hips and his back resting but not locked in that position, thereby allowing compensatory movements, which were also measured (Fig. 2).

Each of the two kinematic evaluations (pre- and post-treatment) were recorded in a session in which the patient was invited to reach and point at the target from a neutral position, without straining, first with the healthy limb and then with the paretic one. Repeating the task six times took about 10 min.

Data processing and statistical analysis
Three-dimensional marker trajectories were recorded using frame-by-frame acquisition software (SMART Capture—BTS, Milan, Italy) and labelled using frame-by-frame
tracking software (SMART Tracker—BTS, Milan, Italy). The captured data were transferred to MATLAB software (The Mathworks Inc., Natick, MA, USA), were interpolated and filtered with a 6 Hz second-order Butterworth filter in both forwards and reverse directions, resulting in a zero-phase distortion and fourth order filtering.

The velocity of the hand marker was computed using numerical differentiation. Movement onset was defined at the time when the velocity of the hand marker exceeded 5% of the maximum velocity in the pointing phase. Movement offset was detected when the velocity of the hand was below the threshold previously described (Alt Murphy, Willén & Sunnerhagen, 2012).

Kinematic data of the session were processed to calculate the following indices:

- Movement time (MT), as the total execution time of the task (between onset and offset), measured in seconds (Cho & Song, 2015; Alt Murphy, 2013; Frisoli et al., 2012; Burgar et al., 2011);
- Peak velocity (PV), as the maximum value of the speed profile curve of the hand marker, measured in meters per second (Alt Murphy, 2013; Subramanian et al., 2010; Coscia et al., 2014; Bartolo et al., 2014; Rigoldi et al., 2012; Menegoni et al., 2009);
- Time to PV (TtPV), as the percentage of time from the beginning of the movement to the peak speed (Alt Murphy, 2013; Rigoldi et al., 2012);
- Normalized Jerk (NJ), as a non-dimensional quantity which corresponds to the square root of the jerk (third derivative of the position of the hand marker with respect to time),

Figure 3 Kinematic model for reflective marker placement adopted in this study. A total of 12 markers (14 mm diameter) are placed over prominent bony landmarks of the upper extremity, easily identifiable, and reproducible, where subcutaneous tissue is thin, minimizing soft tissue artifact due to marker movement with respect to bone.
mediated over the entire duration of the movement, and normalized with respect to MT and to the total displacement of the onset and offsets (L) (Coscia et al., 2014; Bartolo et al., 2014; Bland & Altman, 1994);

- Trunk Displacement (TD), measured in meters to identify compensation movements, calculated as the difference between the maximum displacement of the trunk marker and its initial position in space, normalized with respect to distance C7-sacrum, expressed as a percentage (Alt Murphy, 2013; Subramanian et al., 2010; Coscia et al., 2014);

- Hand Path Ratio (HPR) is the ratio of the distance travelled by the hand between the movement onset and offset and the straight-line distance between the starting and destination targets, expressed as a percentage (Subramanian et al., 2010; Rigoldi et al., 2012; Menegoni et al., 2009; Colombo et al., 2005).

Movement time, PV, and TtPV indices are related to the time required for pointing at the target and the speed at which the task is performed.

Normalized Jerk quantifies the fluidity of motion: higher values correspond to lower smoothness, reflecting poor fluidity in motion, or absence of fine tuning of muscular control, whereas a fluid movement will be expressed by a lower value. Although other indices of smoothness have been proven valuable during the last few years (Balasubramanian et al., 2015), today NJ is the most widely adopted index for smoothness.

Trunk Displacement provides information about the compensation strategies implemented by the patient during execution of the task.

Hand Path Ratio, instead is considered an index of motion accuracy in point-to-point movements (Do Tran, Dario & Mazzoleni, 2018).

Statistical analyses were performed with SPSS software (Statistical Packages for Social Sciences, version 24.0; SPSS Inc., Chicago, IL, USA). Considering the non-normal distribution of the indices and the small size of the sample, non-parametric tests with a 95% confidence interval (α = 0.05) were applied. In particular, the Wilcoxon signed-rank test two-tailed was chosen to verify whether there were differences between pre- and post-treatment for each parameter. The Spearman correlation test was performed to highlight any correlation between kinematic parameters and the main clinical scales used.

RESULTS

An example of reaching trajectories, obtained during the evaluation tasks, is depicted in Fig. 4. Figure 5 reports mean and standard deviation values of the NJ calculated on hand trajectories during each task repetition. Significant differences between pre- and post-treatment kinematic indices were found for MT (Z = −2.701, p = 0.007), NJ (Z = −2.701, p = 0.007), TD (Z = −2.701, p = 0.007), and HPR (Z = −2.701, p = 0.007). The average values of all these parameters were lower after the treatment than before, as reported in Fig. 6. No significant difference was found for PV, and TtPV between the pre- and post-treatment evaluations. As displayed in Figs. 5 and 6, the values of the indices, derived from the affected arm, are reported along with values obtained from the unaffected arm, to visually compare the difference in the indices and illustrate improvement.
All of the administered clinical assessment scales resulted in pre- vs. post-treatment significant decrease: FIM ($Z = -2.803, p = 0.005$), BI ($Z = -2.809, p = 0.005$), FAT ($Z = -2.831, p = 0.005$), FMA ($Z = -2.807, p = 0.005$), as reported in Table 2.

Table 3 reports the results of the Spearman correlation test, across all kinematic parameters and all administered clinical assessment scales. A strong tendentially significant correlation was found between FAT and HPR. A moderate, yet not significant, correlation ($0.40 < |r_s| < 0.59$), was found between BI and MT, BI and TD, FAT and TtPV, and FMA and HPR.
Figure 6 Mean values of the six kinematic indices calculated across all the patients. (A) MT; (B) PV; (C) TtPV; (D) NJ; (E) TD; (F) HPR. Error bars represent the standard deviation (±). For each index, mean values obtained with the affected arm before the treatment are depicted in green. Values obtained with the same arm after the treatment are reported in blue. Statistical significance between the two conditions are starred. For visual comparison, values obtained with the non-affected arm are also reported in yellow.

Table 2 Spearman correlation coefficients and significance level (in brackets) between the four clinical scales score and kinematic parameters, evaluated post-treatment.

| Scale | Pre-treatment | Post-treatment | p value |
|-------|---------------|----------------|---------|
| FIM   | 78.5 ± 19.1   | 98.7 ± 13.6    | 0.005   |
| BI    | 52.5 ± 21.1   | 75.5 ± 14.0    | 0.005   |
| FAT   | 1.5 ± 1.4     | 4.2 ± 1.1      | 0.005   |
| FMA   | 32.6 ± 13.9   | 45 ± 10.7      | 0.005   |

Table 3 Pre-treatment and post-treatment values (mean ± standard deviation) of clinical scales. Superscript T marks tendentially significant values.

| Index | Scale | MT    | PV     | TtPV   | NJ     | TD     | HPR    |
|-------|-------|-------|--------|--------|--------|--------|--------|
|       | FM    | −0.164 (0.650) | 0.024 (0.947) | 0.359 (0.309) | −0.207 (0.567) | −0.140 (0.699) | −0.049 (0.894) |
|       | BI    | −0.470 (0.171) | 0.384 (0.273) | −0.049 (0.894) | −0.396 (0.257) | −0.511 (0.131) | 0.024 (0.947) |
|       | FAT   | −0.192 (0.595) | −0.096 (0.792) | 0.528 (0.117) | −0.329 (0.353) | 0.364 (0.301) | −0.624 T 0.054 |
|       | FMA   | −0.036 (0.920) | −0.120 (0.973) | 0.164 (0.650) | 0 1     | 0.152 (0.674) | −0.426 (0.220) |
DISCUSSION

In this study, we analysed the effects of RMT conducted with an exoskeleton that supported the 3D movement of the upper limbs, involved 10 stroke survivors, using a pre- vs. post-treatment 3D kinematic analysis of a specific upper limb gesture, which mirrored a daily living activity. Their residual motion capabilities were evaluated by means of a set of kinematic parameters that were measured during execution of a reaching task with both the paretic and the unaffected arm, other than by using the four most adopted clinical scales.

Our findings demonstrate the benefits of a rehabilitation programme focused on the range of motion capabilities of post-stroke patients. Indeed, these patients demonstrated an improvement across all administered clinical scales, and these results are in agreement with the kinematic analysis conducted. The trajectories of reaching tasks performed after treatment were smoother and more accurate. Four out of the six kinematic indices computed on the reaching trajectories travelled after the treatment of the paretic arm were different to those obtained before the treatment. In particular, indices obtained with the paretic arm, after the treatment, showed movement more comparable to the unaffected arm.

The significant decrease in MT indicates regained mobility with gesture performance. A reduced time to complete the task implies a more effective combination of motion smoothness and accuracy. Regardless of the actual distribution of improvement from these two aspects, the overall ability to complete the task in a reduced timeframe indicates an increase in patient independence in daily life, which is a key concern in rehabilitation. Frisoli et al. (2012) demonstrated a significant correlation with the total time for the reaching movement with the clinical evaluation of motor impairment in both ischemic and hemorrhagic stroke patients. This index showed a significant decrease after a rehabilitation programme, towards the value observed in healthy control group.

Normalized Jerk is generally understood as an index of motion smoothness, where higher levels of this parameter are typical of less smoothly controlled gestures (Hogan & Sternad, 2009). All of the patients showed a noticeable decrease in the NJ average value in reaching tasks performed with the paretic arm. Values of NJ obtained after the RMT programme, are closer to those performed with the unaffected arm.

Conversely, HPR represents the subject’s ability to perform a reaching trajectory within the shortest possible distance between the start and target points. A line connecting the two points does not exactly represent the path chosen by unimpaired subjects, as shown in Fig. 3. However, the difference between the actual hand trajectory and the line is an important parameter in evaluating accuracy in reaching tasks (Burgar et al., 2011). Stroke survivors who participated in our study exhibited a significant decrease in this index in post-treatment trials compared to pre-treatment ones, with an average value more comparable with that of the unaffected arm.

Another significant improvement was observed in the TD index for our sample study. This result can be interpreted as a secondary effect of the restoration of motor activation paths from the motor cortex to muscles. The increased capability of the subject...
to fire the necessary motor units required less compensatory trunk muscle activity to complete the task (Murphy, Willén & Sunnerhagen, 2010). Murphy, Willén & Sunnerhagen (2010) demonstrated that TD is significantly higher in post-stoke patients than in healthy subjects, and a notable increase in this index can also be observed between patients with moderate stroke with respect to those with a mild stroke.

Interestingly, no significant effect was observed in PV and TtPV. Although these are generally considered indices of motor capability in point-to-point tasks (Alt Murphy, 2013), the patients involved in this study did not exhibit any significant variation in these two indices. The restored motor control, highlighted by other observed markers, both clinical and kinematic, was not reflected in the velocity profile of the hand during specific pointing tasks. Thus, our preliminary findings suggest that one should not simply rely on these two indices as effective measurements for the effectiveness of a rehabilitation programme.

Although the results were obtained from a small patient sample, the findings of the present study are particularly important to current discussions about RMT. Moreover, to date, several studies have assessed improvements in the motion capabilities of stroke survivors after RMT treatments, for a larger cohort of subjects (Lo et al., 2009). However, improvement has mainly been evaluated by means of clinical rating scales or kinematic indices computed on gesture trajectories performed during rehabilitation treatment. Thus, it is generally accepted that training stroke survivors to perform specific upper arm trajectories, in a controlled and assisted manner that is facilitated by a robotic device, leads to improvement in performing a specific task. However, a key issue with motor rehabilitation is the translational effect of therapy, that is the potential to improve gestures typically associated with daily life, distinct from those performed in a rehabilitation programme (Kwakkel et al., 1997). This problem is of great importance in analysing the RMT effect throughout the entire rehabilitation process. Current studies only merely use the robotic device as a therapeutic instrument, while the kinematic evaluation was used to evaluate a simple gesture, which was highly representative of a daily life scenario.

Despite the number of RMT studies conducted thus far, proving increased performance compared to a traditional rehabilitation programme, within the same timeframe, remains a challenge (Norouzi-Gheidari, Archambault & Fung, 2012). One reason is the lack of a standardized evaluation protocol for measuring the impact, apart from the use of clinical scales. Although highly comprehensive and well structured, clinical scales are not an objective tool, and are often comprised of different characteristics related to disability, ranging from motor capabilities to facial expressions or psychological treats. The protocol presented in this study has the potential to serve as a standard evaluation tool for more objectively quantifying upper limb motor smoothness and accuracy, derived from a rehabilitation programme, and ultimately inspiring comparative studies on the efficacy of RMT vs. traditional therapy. Several studies have examined the pointing movement in stroke patients (Alt Murphy, 2013; Frisoli et al., 2012; Subramanian et al., 2010; Duret & Hutin, 2013; Cirstea & Levin, 2000; Nordin, Xie & Wünsche, 2014); however, they have used different kinematic variables to analyse the movement, despite the common goal of being able to quantify speed, accuracy and fluidity of movement.
In this vein, a comparative analysis of patient behaviour in kinematic evaluation, in terms of clinical scales score, is of great importance.

The kinematic evaluation protocol that we adopted, instead, was introduced by Caimmi et al. (2007), to evaluate the effects of constraint-induced therapy. In this study, we used this method to evaluate effects of RMT sessions, performed using a rehabilitation exoskeleton that induces 3D movements of the upper limb. Reporting these findings is valuable as the literature is lacking when it comes to these types of studies, especially with RMT solutions inducing planar movements, where the gravity effect is completely supported. The adoption of 3D robotics, assisting the subjects in compensating for gravity, is expected to enhance this capability.

To consolidate the preliminary findings of this study, and positively contribute to the current discussions about the impact of RMT, future studies should involve a larger patient sample, in parallel with a control group undergoing conventional therapy. If confirmed on a larger number of patients, the positive results reported herein will pave the way for the establishment of a standardized procedure for objectively evaluating motor recovery in conjunction with a robotic rehabilitation programme. This tool would have a tremendous potential in facilitating comparative studies about the effects of RMT compared to traditional physical therapy for rehabilitation.

Moreover, apart from the advantaged documented in this paper, as in other similar studies, it is not possible to isolate the effects of RMT per se. A physiological progressive improvement in the motor capabilities of stroke survivors, during the subacute phase, has already been demonstrated (Van Kordelaar, Van Wegen & Kwakkel, 2014). Thus, a comparative study with only two groups of stroke survivors would be required, where one group is treated with RMT, which would accurately quantify the benefits of RMT, although this would be questionable in terms of ethics. Ultimately, reporting the results of a specific therapy, using a standard protocol and a set of accepted indices, is valuable, as it permits a better interpretation of the actual outcomes of the therapy.

CONCLUSIONS

In this study, we analysed the effects of robot-mediated therapy on 10 stroke survivors, through a pre- vs. post-treatment 3D kinematic analysis of a specific upper limb gesture, simulating ADL. Their residual motion capabilities were evaluated by means of a set of kinematic parameters measured during the execution of a reaching task with both a paretic and an unaffected arm.

Our results highlighted the efficacy of a rehabilitation programme that benefits the motion capabilities of patients. Patients exhibited improvements in all of the administered clinical scales, which was in agreement with the kinematic analysis conducted.

Although the analysis was obtained from a small sample of patients, the findings of our study have the potential to contribute to the current discussions about robot-mediated therapy. The protocol presented in this study, inspired by daily-life gestures (upper limb motor tasks), may represent a step forwards in establishing a standard evaluation procedure, for the objective quantification of upper limb motor recovery following RMT-based treatments.
ADDITIONAL INFORMATION AND DECLARATIONS

Funding
The authors received no funding for this work.

Competing Interests
The authors declare that they have no competing interests.

Author Contributions
- Eduardo Palermo conceived and designed the experiments, analyzed the data, contributed reagents/materials/analysis tools, prepared figures and/or tables, authored or reviewed drafts of the paper, approved the final draft.
- Darren Richard Hayes conceived and designed the experiments, analyzed the data, contributed reagents/materials/analysis tools, authored or reviewed drafts of the paper, approved the final draft.
- Emanuele Francesco Russo conceived and designed the experiments, performed the experiments, analyzed the data, contributed reagents/materials/analysis tools, prepared figures and/or tables, authored or reviewed drafts of the paper, approved the final draft.
- Rocco Salvatore Calabrò conceived and designed the experiments, contributed reagents/materials/analysis tools, authored or reviewed drafts of the paper, approved the final draft.
- Alessandra Pacilli conceived and designed the experiments, contributed reagents/materials/analysis tools, authored or reviewed drafts of the paper, approved the final draft.
- Serena Filoni conceived and designed the experiments, performed the experiments, contributed reagents/materials/analysis tools, authored or reviewed drafts of the paper, approved the final draft.

Human Ethics
The following information was supplied relating to ethical approvals (i.e. approving body and any reference numbers):
This study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committees of IRCCS Centro neurolesi Bonino Pulejo (study registration number 43/2013).

Data Availability
The following information was supplied regarding data availability:
The raw data are also provided in a Supplemental File.

Supplemental Information
Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj.5544#supplemental-information.

REFERENCES
Alt Murphy M. 2013. Development and validation of upper extremity kinematic movement analysis for people with stroke reaching and drinking from a glass. Doctoral thesis, Institute of Neuroscience and Physiology, Department of Clinical Neuroscience and Rehabilitation, University of Gothenburg.
Alt Murphy M, Willén C, Sunnerhagen KS. 2012. Movement kinematics during a drinking task are associated with the activity capacity level after stroke. *Neurorehabilitation and Neural Repair* 26(9):1106–1115 DOI 10.1177/1545968312448234.

Balasubramanian S, Melendez-Calderon A, Roby-Brami A, Burdet E. 2015. On the analysis of movement smoothness. *Journal of NeuroEngineering and Rehabilitation* 12(1):112 DOI 10.1186/s12984-015-0090-9.

Bartolo M, De Nunzio AM, Sebastiano F, Spicciato F, Tortola P, Nilsson J, Pierelli F. 2014. Arm weight support training improves functional motor outcome and movement smoothness after stroke. *Functional Neurology* 29(1):15–21 DOI 10.11138/fneur/2014.29.1.015.

Bland JM, Altman DG. 1994. One and two sided tests of significance. *BMJ* 309(6949):248.

Bosecker C, Dipietro L, Volpe B, Krebs HI. 2009. Kinematic robot-based evaluation scales and clinical counterparts to measure upper limb motor performance in patients with chronic stroke. *Neurorehabilitation and Neural Repair* 24(1):62–69 DOI 10.1177/1545968309343214.

Burgar CG, Lum PS, Scremin AME, Garber SL, Van Der Loos HFM, Kenney D, Shor P. 2011. Robot-assisted upper-limb therapy in acute rehabilitation setting following stroke: Department of Veterans Affairs multisite clinical trial. *Journal of Rehabilitation Research and Development* 48(4):445–458 DOI 10.1682/jrrd.2010.04.0062.

Caimmi M, Carda S, Giovananza C, Maini S, Sabatini AM, Smania N, Molteni F. 2007. Using kinematic analysis to evaluate constraint-induced movement therapy in chronic stroke patients. *Neurorehabilitation and Neural Repair* 22(1):31–39 DOI 10.1177/1545968307302923.

Calabrò RS, Russo M, Naro A, Milardi D, Balletta T, Leo A, Filoni S, Bramanti P. 2016. Who may benefit from armeo power treatment? A neurophysiological approach to predict neurorehabilitation outcomes. *PM&R* 8(10):971–978 DOI 10.1016/j.pmrj.2016.02.004.

Cho KH, Song W-K. 2015. Robot-assisted reach training for improving upper extremity function of chronic stroke. *Tohoku Journal of Experimental Medicine* 237(2):149–155 DOI 10.1620/tjem.237.149.

Cirstea MC, Levin MF. 2000. Compensatory strategies for reaching in stroke. *Brain* 123(S):940–953 DOI 10.1093/brain/123.5.940.

Colombo R, Pisano F, Micera S, Mazzone A, Delconte C, Carrozza MC, Dario P, Minuco G. 2005. Robotic techniques for upper limb evaluation and rehabilitation of stroke patients. *IEEE Transactions on Neural Systems and Rehabilitation Engineering* 13(3):311–324 DOI 10.1109/tnsre.2005.848352.

Colombo R, Sterpi I, Mazzone A, Delconte C, Pisano F. 2013. Robot-aided neurorehabilitation in sub-acute and chronic stroke: does spontaneous recovery have a limited impact on outcome? *NeuroRehabilitation* 33(4):621–629.

Coscia M, Cheung VC, Tropea P, Koenig A, Monaco V, Bennis C, Micera S, Bonato P. 2014. The effect of arm weight support on upper limb muscle synergies during reaching movements. *Journal of NeuroEngineering and Rehabilitation* 11(1):22 DOI 10.1186/1743-0003-11-22.

Do Tran V, Dario P, Mazzoleni S. 2018. Kinematic measures for upper limb robot-assisted therapy following stroke and correlations with clinical outcome measures: a review. *Medical Engineering & Physics* 53:13–31 DOI 10.1016/j.medengphy.2017.12.005.

Duret C, Hutin E. 2013. Effects of prolonged robot-assisted training on upper limb motor recovery in subacute stroke. *NeuroRehabilitation* 33(1):41–48.

Frisoli A, Procopio C, Chisari C, Creatini I, Bonfiglio L, Bergamasco M, Rossi B, Carboncini M. 2012. Positive effects of robotic exoskeleton training of upper limb reaching movements after stroke. *Journal of NeuroEngineering and Rehabilitation* 9(1):36 DOI 10.1186/1743-0003-9-36.
Heller A, Wade DT, Wood VA, Sunderland A, Hewer RL, Ward E. 1987. Arm function after stroke: measurement and recovery over the first three months. *Journal of Neurology, Neurosurgery & Psychiatry* 50(6):714–719 DOI 10.1136/jnnp.50.6.714.

Hogan N, Krebs HI, Charnnarong J, Srikrishna P, Sharon A. 1992. MIT-MANUS: a workstation for manual therapy and training I. In: (1992) Proceedings IEEE international workshop on robot and human communication. Piscataway: IEEE, 161–165.

Hogan N, Krebs HI, Charnnarong J, Srikrishna P, Sharon A. 1993. MIT-MANUS: a workstation for manual therapy and training II. In: *Applications in Optical Science and Engineering*. Vol. 1833. Bellingham: Society of Photo-Optical Instrumentation Engineers (SPIE), 28–34.

Hogan N, Sternad D. 2009. Sensitivity of smoothness measures to movement duration, amplitude, and arrests. *Journal of Motor Behavior* 41(6):529–534 DOI 10.3200/35-09-004-rc.

Kahn L, Lum P, Rymer W, Reinkensmeyer D. 2006. Robot-assisted movement training for the stroke-impaired arm: does it matter what the robot does? *Journal of Rehabilitation Research and Development* 43(5):619 DOI 10.1682/jrrd.2005.03.0056.

Kwakkel G, Wagenaar RC, Koelman TW, Lankhorst GJ, Koetsier JC. 1997. Effects of intensity of rehabilitation after stroke: a research synthesis. *Stroke* 28(8):1550–1556 DOI 10.1161/01.str.28.8.1550.

Liao W, Wu C, Hsieh Y, Lin K, Chang W. 2012. Effects of robot-assisted upper limb rehabilitation on daily function and real-world arm activity in patients with chronic stroke: a randomized controlled trial. *Clinical Rehabilitation* 26(2):111–120 DOI 10.1177/0269215511416383.

Lo AC, Guarino P, Krebs HI, Volpe BT, Bever CT, Duncan PW, Ringer RJ, Wagner TH, Richards LG, Bravata DM, Haselkorn JK, Wittenberg GF, Federman DG, Corn BH, Maffucci AD, Peduzzi P. 2009. Multicenter randomized trial of robot-assisted rehabilitation for chronic stroke: methods and entry characteristics for VA ROBOTICS. *Neurorehabilitation and Neural Repair* 23(8):775–783 DOI 10.1177/1545968309338195.

Masiero S, Celia A, Rosati G, Armani M. 2007. Robotic-assisted rehabilitation of the upper limb after acute stroke. *Archives of Physical Medicine and Rehabilitation* 88(2):142–149 DOI 10.1016/j.apmr.2006.10.032.

McCrea PH, Eng JJ, Hodgson AJ. 2002. Biomechanics of reaching: clinical implications for individuals with acquired brain injury. *Disability and Rehabilitation* 24(10):534–541 DOI 10.1080/096382801101115393.

Menegoni F, Milano E, Trotti C, Galli M, Bigoni M, Baudo S, Mauro A. 2009. Quantitative evaluation of functional limitation of upper limb movements in subjects affected by ataxia. *European Journal of Neurology* 16(2):232–239 DOI 10.1111/j.1468-1331.2008.02396.x.

Mihelj M, Nef T, Riener R. 2006. ARMin—Toward a six DoF upper limb rehabilitation robot. In: *The first IEEE/RAS-EMBS international conference on biomedical robotics and biomechatronics*, 2006. Piscataway: IEEE, 1154–1159.

Murphy MA, Willén C, Sunnerhagen KS. 2010. Kinematic variables quantifying upper-extremity performance after stroke during reaching and drinking from a glass. *Neurorehabilitation and Neural Repair* 25(1):71–80 DOI 10.1177/1545968310370748.

Nef T, Mihelj M, Colombo G, Riener R. 2006. ARMin—robot for rehabilitation of the upper extremities. In: *Proceedings 2006 IEEE International conference on Robotics and Automation*, 2006. Vol. 3. Piscataway: IEEE, 3152–3157.
Nordin N, Xie S, Wünsche B. 2014. Assessment of movement quality in robot-assisted upper limb rehabilitation after stroke: a review. *Journal of NeuroEngineering and Rehabilitation* 11(1):137 DOI 10.1186/1743-0003-11-137.

Norouzi-Gheidari N, Archambault PS, Fung J. 2012. Effects of robot-assisted therapy on stroke rehabilitation in upper limbs: systematic review and meta-analysis of the literature. *Journal of Rehabilitation Research and Development* 49(4):479–496 DOI 10.1682/jrrd.2010.10.0210.

Panarese A, Pirondini E, Tropea P, Cesqui B, Posteraro F, Micera S. 2016. Model-based variables for the kinematic assessment of upper-extremity impairments in post-stroke patients. *Journal of NeuroEngineering and Rehabilitation* 13(1):81 DOI 10.1186/s12984-016-0187-9.

Papaleo E, Zollo L, García-Aracil N, Badesa FJ, Morales R, Mazzoleni S, Sterzi S, Guglielmelli E. 2015. Upper-limb kinematic reconstruction during stroke robot-aided therapy. *Medical & Biological Engineering & Computing* 53(9):815–828 DOI 10.1007/s11517-015-1276-9.

Parker VM, Wade DT, Hewer RL. 1986. Loss of arm function after stroke: measurement, frequency, and recovery. *International Rehabilitation Medicine* 8(2):69–73 DOI 10.3109/03790798609166178.

Prange GB, Jannink MJA, Groothuis-Oudshoorn CGM, Hermens HJ, IJzerman MJ. 2006. Systematic review of the effect of robot-aided therapy on recovery of the hemiparetic arm after stroke. *Journal of Rehabilitation Research and Development* 43(2):171–184 DOI 10.1682/jrrd.2005.04.0076.

Rab G, Petuskey K, Bagley A. 2002. A method for determination of upper extremity kinematics. *Gait & Posture* 15(2):113–119 DOI 10.1016/s0966-6362(01)00155-2.

Rahman HA, Xiang KK, Tai YC, Ming ESL, Narayanan AL. 2016. Robotic assessment modules for upper limb stroke assessment: preliminary study. *Journal of Medical Imaging and Health Informatics* 6(1):157–162 DOI 10.1166/jmihi.2016.1608.

Reinkensmeyer DJ. 2003. How to retrain movement after neurologic injury: a computational rationale for incorporating robot (or therapist) assistance. In: *Proceedings of the 25th annual international conference of the IEEE engineering in medicine and biology society (IEEE Cat. No. 03CH37439)*. Piscataway: IEEE, 1479–1482.

Rigoldi C, Molteni E, Rozbaczylo C, Morante M, Albertini G, Bianchi AM, Galli M. 2012. Movement analysis and EEG recordings in children with hemiplegic cerebral palsy. *Experimental Brain Research* 223(4):517–524 DOI 10.1007/s00221-012-3278-2.

Rohrer B, Fasoli S, Krebs H, Hughes R, Volpe B, Frontera WR, Stein J, Hogan N. 2002. Movement smoothness changes during stroke recovery. *Journal of Neuroscience* 22(18):8297–8304 DOI 10.1523/jneurosci.22-18-08297.2002.

Squeri V, Basteris A, Sanguineti V. 2011. Adaptive regulation of assistance ‘as needed’ in robot-assisted motor skill learning and neuro-rehabilitation. In: *2011 IEEE International conference on rehabilitation robotics*. Piscataway: IEEE.

Stein J. 2004. Motor recovery strategies after stroke. *Topics in Stroke Rehabilitation* 11(2):12–22 DOI 10.1310/rk4a-6etg-k8rl-3xa7.

Subramanian SK, Yamanaka J, Chilingaryan G, Levin MF. 2010. Validity of movement pattern kinematics as measures of arm motor impairment poststroke. *Stroke* 41(10):2303–2308 DOI 10.1161/strokeaha.110.593368.

Sullivan KJ, Tilson JK, Cen SY, Rose DK, Hershberg J, Correa A, Gallichio J, McLeod M, Moore C, Wu SS, Duncan PW. 2011. Fugl-Meyer assessment of sensorimotor function after stroke: standardized training procedure for clinical practice and clinical trials. *Stroke* 42(2):427–432 DOI 10.1161/strokeaha.110.592766.
Turner DL, Ramos-Murguialday A, Birbaumer N, Hoffmann U, Luft A. 2013. Neurophysiology of robot-mediated training and therapy: a perspective for future use in clinical populations. *Frontiers in Neurology* 4:184 DOI 10.3389/fneur.2013.00184.

Van Kordelaar J, Van Wegen E, Kwakkel G. 2014. Impact of time on quality of motor control of the paretic upper limb after stroke. *Archives of Physical Medicine and Rehabilitation* 95(2):338–344 DOI 10.1016/j.apmr.2013.10.006.

Vos T, Allen C, Arora M, Barber RM, Bhutta ZA, Brown A, Carter A, Casey DC, Charlson FJ, Chen AZ, Coggeshall M, Cornaby L, Dandona L, Dicker DJ, Direige T, Erskine HE, Ferrari AJ, Fitzmaurice C, Fleming T, Forouzanfar MH, Fullman N, Gething PW, Goldberg EM, Graetz N, Haagsma JA, Hey SI, Johnson CO, Kasaebeamn JA, Kawashima T, Kemmer L, Khalil IA, Kinfu Y, Kyu HH, Leung J, Liang X, Lim SS, Lopez AD, Lozano R, Marczak L, Mensah GA, Mokdad AH, Naghavi M, Nguyen G, Nseroe ES, Olsen H, Pigott DM, Pinho C, Rankin Z, Reinig N, Salomon JA, Sandar L, Smith A, Stanaway J, Steiner C, Teeple S, Thomas BA, Troeger C, Wagner J, Wang H, Wanga V, Whiteford HA, Zockler L, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, Abraham B, Abubakar I, Abu-Raddad LJ, Abu-Rmeileh NME, Ackerman IN, Adabiyi AO, Ademi Z, Adou AK, Afanvi KA, Agardh EE, Agarwal A, Kiadaliria AA, Ahmadieh H, Ajala ON, Akinyemi RO, Akeer N, Al-Aly Z, Alam K, Alam NK, Aldhahri SF, Alegratti MA, Alemu ZA, Alexander LT, Alhabib S, Ali R, Alkerwi A, Alla F, Allebeck P, Al-Raddadi R, Alsharif U, Altirkawi KA, Alvis-Guzman N, Amare AT, Amberbir A, Amini H, Ammar W, Amrock SM, Andersen HH, Anderson GM, Anderson BO, Antonio CAT, Aregay AF, Årnlov J, Artaman A, Asayesh H, Assadi R, Atique S, Avokpahoo EFGA, Avgasti A, Quintanilla BPA, Azzopardi P, Bacha U, Badawi A, Balakrishnan K, Banerjee A, Barac A, Barker-Collo SL, Bärnighausen T, Barrеро LH, Basu A, Bazzarag-Hejazi S, Beghi E, Bell B, Bell ML, Bennett DA, Bensenor IM, Benzian H, Berhane A, Bernabé E, Betus BD, Beyene AS, Bhala N, Bhatt S, Biadgilign S, Bijnhoff K, Bikbov B, Birukov S, Bisanzio D, Bjertnes E, Blore J, Borschmann R, Boufous S, Brainin M, Brazina L, Bovtseborde NJK, Brown J, Buchbinder R, Buckle GC, Butt ZA, Calabria B, Campos-Nonato IR, Campuzano JC, Carabin H, Cárdenas R, Carpenter DO, Carrero JJ, Castañeda-Orjuela CA, Civas JC, Catalá-López F, Chang J-C, Chiang PP-C, Chibueze CE, Chisumpa VH, Choi J-YJ, Chowdhury R, Christensen H, Christopher DJ, Ciobanu LG, Cirillo M, Coates MM, Colquhoun SM, Cooper C, Cortinovis M, Crump JA, Damtew SA, Dandona R, Daoud F, Dargan PI, Das Neve S, Davey G, Davis AC, De Leo D, Degenhardt L, Del Gobbo LC, Dellavalle RP, Deribe K, Deribew A, Derrett S, Des Jarlais DC, Dharmaratne SD, Dhillon PK, Diaz-Torné C, Ding EL, Driscoll TR, Duan L, Dubey M, Duncan BB, Ebrapim H, Ellenbogen RG, Elyazar I, Endres M, Endries AY, Ermakov SP, Esrati B, Estep K, Farid TA, Farinaha CSeS, Faro A, Farvid MS, Farzadfar F, Feigin VL, Felson DT, Fereshtehnejad S-M, Fernandes JG, Fernandes JC, Fischer F, Fitchett JRA, Foreman K, Fowkes FGR, Fox J, Franklin RC, Friedman J, Frostad J, Fürst T, Futran ND, Gabbe B, Ganguly P, Gampé FG, Gebre T, Gebrehiwot TGT, Gebremedhin AT, Geleijnse J, Gessner BD, Gibney KB, Ginawi IAM, Giref AZ, Giroud M, Gishu MD, Giussani G, Glaser E, Godwin WW, Gomez-Dantes H, Gona P, Goodridge A, Gopalan SV, Gotay CC, Goto A, Gouda HN, Grainger R, Greaves F, Guillemin F, Guo Y, Gupta R, Gupta R, Gupta V, Guizhertw RA, Harle D, Halin AD, Halilu GB, Halasa YA, Hamadeh RR, Hamidi S, Hammami M, Hancock J, Handal AJ, Hankey GJ, Hao Y, Harb HL, Harikrishnan S, Haro JM, Havmoeller R, Hay RJ, Heredia-Pi IB, Heydarpour P, Hoek HW, Horino M, Horita N, Hosgood HD, Hoy DG, Hüet AS, Huang H, Huang JJ, Huynh C, Iannarone MA, Iburg KM, Innos K, Inoue M, Iyer VJ, Jacobsen KH, Jahnmehr N, Jakovljevic MB, Javanbakht M, Jayaraman SP, Jayatilleke AU, Jee SH, Jeemon P, Jensen PN, Jiang Y, Jibat T,
Jimenez-Corona A, Jin Y, Jonas JB, Kabir Z, Kalkonde Y, Kamal R, Kan H, Karch A, Karem CK, Karimkhani C, Kasaean A, Kaul A, Kawakami N, Keiyoro PN, Kemp AH, Keren A, Kesavachandran CN, Khader YS, Khan AR, Khan EA, Khyang Y-H, Khera S, Khoja TAM, Khubchandani J, Kieling C, Kim P, Kim C, Kim D, Kim YJ, Kissoon N, Knibbs LD, Knudsen AK, Kokubo Y, Kolte D, Kopec JA, Kosen S, Kotsakis GA, Koul PA, Koyanagi A, Kravchenko M, Defo BK, Bicer BK, Kudom AA, Kuipers EJ, Kumar GA, Kutz M, Kwan GF, Lal A, Laloo R, Lallukka T, Lam H, Lam JO, Langan SM, Larsson A, Lavados PM, Leasher JL, Leigh J, Leung R, Levi M, Li Y, Li Y, Liang J, Liu S, Liu Y, Lloyd BK, Lo WD, Logroscino G, Loozer MJ, Lotufo PA, Lunevicius R, Lyons RA, Mackay MT, Magdy M, El Razek A, Mahdavi M, Majdan M, Majeed A, Malekzadeh R, Marcenes W, Margolis DJ, Martinez Raga J, Masiyi F, Massano J, McGarvey ST, McGrath JJ, McKee M, McMahon BJ, Meaney PA, Mehari A, Mejia-Rodriquez F, Mekonnen AB, Melaku YA, Memiah P, Memish ZA, Mendoza W, Meretoja A, Meretoja TJ, Mhimbira FA, Millaer A, Miller TR, Mills EJ, Mirafini M, Mitchell PB, Mock CN, Mohammadi A, Mohammed S, Monasta L, Hernandez JCM, Montico M, Mooney MD, Moradi-Lakeh M, Morawska L, Mueller UO, Mullany E, Mumford JE, Murdoch ME, Nabeta J, Nagel G, Naheed A, Naldi L, Nangia V, Newton JN, Ng M, Ngalesoni FN, Le Nguyen Q, Nisar MI, Pete PMN, Nolla JM, Norheim OF, Norman RE, Norrving B, Nunes BP, Ogbo FA, Oh I-H, Okhobo T, Oliwaes PR, Olusanya BO, Olusanya JO, Ortiz A, Osman M, Ota E, Pa M, Park E-K, Parsaean M, De Azeredo Passos VM, Caicedo AJP, Patten SB, Patton GC, Pereira DM, Perez Padilla R, Perico N, Pesudovs K, Petzold M, Phillips MR, Piel FB, Pillay JD, Pishgar F, Plass D, Platts Mills JA, Polinder S, Pond CD, Popova S, Poulton RG, Pourmalek F, Prabhakaran D, Prasad NM, Qorbani M, Rabie R, Rafay A, Rahimi K, Rahimi Movaghar V, Rahman M, Rahman MTH, Rahman SU, Rai RK, Rajisic S, Ram U, Rao P, Refaat AH, Reitmaier J, Remuzzi G, Resnikoff S, Reynolds A, Ribeiro AI, Blancas MJR, Roba HS, Rojas Rueda D, Ronfani L, Roosendal G, Roth GA, Rothenbacher D, Roy A, Sagar R, Sahatheyvan R, Sanabria JR, Sanchez Niño MD, Santos IS, Santos JV, Sarmento Suarez R, Sartorius B, Satpathy M, Savic M, Sawhney M, Schaub MP, Schmidt MI, Schneider IJC, Schöttker B, Schwabe DC, Scott JG, Seedat S, Sepanlou SG, Servan Mori EE, Shackelford KA, Shaheen A, Shaikh MA, Sharma R, Sharma U, Shen J, Shepard DS, Sheth KN, Shibuya K, Shin M-J, Shiri R, Shiue I, Shrive MG, Sigfusdottir ID, Silva DAS, Silveira DGA, Singh A, Singh JA, Singh OP, Singh PK, Sivoda A, Skirbekk V, Skogen JC, Sliwa K, Soljak M, Soreide K, Sorensen RJD, Soriano JB, Sposato LA, Sreearameddy CT, Stathopoulos V, Steel N, Stein DJ, Steininger T, Steinke S, Stovner L, Stroumpoulis K, Sunguya BF, Sur P, Swaminathan S, Sykes BL, Szoeke CEI, Tabarés Seixedas R, Takala JS, Tandon N, Tanne D, Tavakkoli M, Taye B, Taylor HR, Te Ao BJ, Tedla BA, Terkawi AS, Thomson AJ, Thornleyman AL, Thrift AG, Thurston GD, Tobe Gai R, Tonelli M, Topor Madry R, Topouzis F, Tran BX, Truelsen T, Dimbuene ZT, Tsilimbaris M, Tura AK, Tuzcu EM, Tyrovolas S, Ukwaja KN, Undurraga EA, Uneke CJ, Uthman OA, Van Goor CH, Varakin YY, Vasankari T, Venketasubramanian N, Verma RK, Violante FS, Vladimirov SK, Vlassov VV, Vollset SE, Wagner GR, Waller SG, Wang L, Watkins DA, Weichert S, Weiderpass E, Weintraub RG, Werdecker A, Westerman R, White RA, Williams HC, Wijesinghe CS, Wolfe CDA, Won S, Woodward R, Wubsheh M, Xavier D, Xu G, Yadav AK, Yan LL, Yano Y, Yasermi M, Ye P, Yeho HG, Yip P, Yonemoto N, Yoon S-J, Younis MZ, Yu C, Zaidi Z, Zaki MES, Zaki ME, Zeb H, Zhou M, Zdopsey S, Zuhlike LJ, Murray C JL. 2016. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet 388(10053):1545–1602. DOI 10.1016/S0140-6736(16)31678-6.
Larsson A, Lawrynowicz AE, Leasher JL, Lee J-T, Leigh J, Leung R, Levi M, Li B, Li Y, Li Y, Liang J, Lim S, Lin H-H, Lind M, Lindsay MP, Lipshultz SE, Liu S, Lloyd BK, Ohno SL, Logroscino G,Looker KJ, Lopez AD, Lopez-Olmedo N, Lortet-Tieulent J, Lotufo PA, Low N, Lucas RM, Lunevicius R, Lyons RA, Ma J, Ma S, Mackay MT, Majdan M, Malekzadeh R, Mapoma CC, Marcenes W, March LM, Margono C, Marks GB, Marzan MB, Masci JR, Mason-Jones AJ, Matzopoulos RG, Mayosi BM, Mazorodze TT, McGill NW, McGrath JJ, McKee M, McLain A, McMahon BJ, Meaney PA, Mehdiratta MM, Mejia-Rodriguez F, Mekonnen W, Melaku YA, Meltzer M, Memish ZA, Mensah G, Meretoja A, Mhimbira FA, Micha R, Miller TR, Mills EJ, Mitchell PB, Mock CN, Moffitt TE, Ibrahim NM, Mohammad KA, Mokdad AH, Mola GL, Monasta L, Montico M, Montine TJ, Moore AR, Moran AE, Morawska L, Mori R, Mosandreas J, Moturi WN, Moyer M, Mozaffarian D, Mueller UO, Mukaiyawara M, Murdoch ME, Murray J, Murthy KS, Naghavi P, Nahas Z, Naheed A, Naidoo KS, Naldi L, Nand D, Nangia V, Narayan KMV, Nash D, Nejati C, Neupane SP, Newman LM, Newton CR, Ng M, Ngalesoni FN, Nhung NT, Nisar MI, Nolte S, Norheim OF, Norman RE, Norrving B, Nyakarahuka L, Oh IH, Ohkubo T, Omer SB, Opio JN, Ortiz A, Pandian JD, Panelo CIA, Papachristou C, Park E-K, Parry CD, Caicedo AJP, Patton SB, Paul VK, Pavlin BI, Pearce N, Pedraza LS, Pellegrini CA, Pereira DM, Perez-Ruiz FP, Perico N, Pervaiz A, Pesudovs K, Peterson CB, Petzold M, Phillips MR, Phillips D, Phillips B, Piel FB, Plass D, Poenaru D, Polanczyk GV, Polinder S, Pope CA, Popova S, Poulton RG, Pourmalek F, Prabhakaran D, Prasad NM, Qato D, Quistberg DA, Rafay A, Rahimi K, Rahimi-Movaghar V, ur Rahman S, Rahuji M, Rakovac I, Rana SM, Razavi H, Refaat A, Rehm J, Remuzzi G, Resnikoff S, Ribeiro AL, Riccio PM, Richardson L, Richardus JH, Riederer AM, Robinson M, Roca A, Rodriguez A, Rojas-Rueda D, Ronfani L, Rothenbacher D, Roy N, Ruhago GM, Sabin N, Sacco RL, Ksoreide K, Saha S, Sahathevan R, Sahraian MA, Sampson U, Sanabria JR, Sanchez-Riera L, Santos IS, Satpathy M, Saunders JE, Sawhney M, Saynali M, Scarborough P, Schoettker B, Schneider IJ, Schwebel DC, Scott JG, Seedat S, Sepanlou SG, Serdar B, Servan-Mori EE, Shackelford K, Shaheen A, Shairaz S, Levy TS, Shangguan S, She J, Sheikhbahaei S, Shepard DS, Shi P, Shibuya K, Shinohara Y, Shiri R, Shishani K, Shiue I, Shride MG, Sigfusdottir ID, Silberberg DH, Simard EP, Sindi S, Singh JA, Singh L, Skirbekk V, Sliwa K, Soljak M, Soneji S, Soshnikov SS, Speyer P, Sposato LA, Sreearamreddy CT, Stoeckl H, Statthopoulou VK, Steckling N, Stein MB, Stein DJ, Steiner TJ, Stewart A, Stork E, Stovner Lj, Stroumpoulis K, Sturua L, Sunugya BF, Swaroop M, Sykes BL, Tabb KM, Takahashi K, Tan F, Tandon N, Tanne D, Tanner M, Tavakkoli M, Taylor HR, Te Ao BJ, Temesgen AM, Ten Have M, Tenkorang EY, Terekas A, Theadom AM, Thomas E, Thorne-Lyman AL, Thrigat AG, Tleyjeh IM, Tonelli M, Topouzis F, Towbin JA, Toyoshima H, Traebert J, Tran BX, Trasande L, Trillini M, Truelsen T, Trujillo U, Tsilimbaris M, Tuzcu EM, Ukwaja KN, Undurraga EA, Uzun SB, Van Brakel WK, Van De Vijver S, Van Dingenen R, Van Gool CH, Varakini TJ, Vavilala MS, Veerman LJ, Velasquez-Melendez G, Venketasubramanian N, Vijayakumar L, Villalpando S, Violante FS, Vlassov VV, Waller S, Wallin MT, Wan X, Wang L, Wang J, Wang S, Warrour TS, Weichenthal S, Weiderpass E, Weintraub RG, Werdecker A, Wessells KRR, Westerman R, Wilkinson JD, Williams HC, Williams TN, Woldeyohannes SM, DA Wolfe C, Wong JQ, Wong H, Woolf AD, Wright JL, Wurtz B, Xu G, Yang G, Yano Y, Yenesew MA, Yentur GK, Yip P, Yonemoto N, Yoon S-J, Younis M, Yu C, Kim KY, Zaki MES, Zhang Y, Zhao Z, Zhao Y, Zhu J, Zonies D, Zunt JR, Salomon JA, Murray CJ. 2015. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic
Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, Casey DC, Charlson FJ, Chen AZ, Coates MM, Coggshall M, Dandona L, Dicker DJ, Erskine HE, Ferrari AJ, Fitzmaurice C, Foreman K, Forouzanfar MH, Fraser MS, Fullman N, Gething PW, Goldberg EM, Graetz N, Haagsma JA, Hay SI, Huynh C, Johnson CO, Kassebaum NJ, Kinfu Y, Kulkoff XR, Kutz M, Kyu HH, Larson HJ, Leung J, Liang X, Lim SS, Lind M, Lozano R, Marquez N, Mensah GA, Mikesell J, Mokdad AH, Mooney MD, Nguyen G, Nsoesie E, Pigott DM, Pinho C, Roth GA, Salomon JA, Sandar L, Silpakit N, Sigrar A, Sorensen RJ, Stanaway J, Steiner C, Teeple S, Thomas BA, Troeger C, VanderZanden A, Vollset SE, Wang V, Whiteford HA, Wolok T, Zoekcller L, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, Abere SF, Abreu DMX, Abu-Raddad LJ, Abyu GY, Achoki T, Adelekan AL, Adeni Z, Adou AK, Adsuar JC, Afanvi KA, Afshin A, Agarhd EE, Agarwal A, Agravai A, Kiadaliri AA, Ajala ON, Akanda AS, Akinyemi RO, Akinyemiju TF, Akseer N, Al Lami FH, Alaped S, Al-Aly Z, Alam K, Alam NKM, Alasfoor D, Aldahari SF, Aldridge RW, Alegretti MA, Aleman AV, Alemu ZA, Alexander LT, Alhabib S, Ali R, Alkerwi A, Alla F, Allebeck P, Al-Raddadi R, Alsharif U, Altirkawi KA, Martin EA, Alviz-Guzman N, Amare AT, Amegah AK, Ameh EA, Aminin H, Ammar W, Amrock SM, Andersen HH, Anderson BO, Anderson GM, Antonio CAT, Aregay AF, Arnlov J, Arsenjevic VSA, Artaman A, Asayesh H, Asghar RJ, Atique S, Avokpah EFGA, Awasthi A, Azzopardi P, Bacha U, Badawi A, Bahia MC, Balakrishnan K, Banerjee A, Barac A, Barker-Collo SL, Barnighausen T, Barregard L, Barrero LH, Basu A, Basu S, Bayou YT, Bazargan-Hejazi S, Beardsley J, Bedi N, Beghi E, Belay HA, Bell B, Bell ML, Bello AK, Bennett DA, Bensenor IM, Berhane A, Bernabe E, Betsu BD, Beyene AS, Bhala N, Bhalla A, Biaodgilign S, Bikbov B, Bin Abdulhak AA, Birosck B, Bjurkoy S, Bjertness E, Blore JD, Blosser CD, Bohensky MA, Borschmann R, Bose D, Bourne RRA, Brainin M, Brayne CEG, Brazinova A, Breitborde NJK, Brenner H, Brewer JD, Brown A, Brown J, Brugha TS, Buckle GC, Butt ZA, Calabria B, Campos-Nonato IR, Campuzano JC, Carapetis JR, Cárdenas R, Carpenter DO, Carrero JJ, Castañeda-Orjuela CA, Rivas JC, Catalá-López F, Cavalleri F, Cercy K, Cerda J, Chen W, Chemp A, Chiang PP-C, Chibalabala M, Chibueze CE, Chimed-Ochir O, Chisumpa VH, Choi J J-Y, Chowdhury H, Christensen H, Christopher DJ, Ciobanu LG, Cirillo M, Cohen AJ, Colistro V, Colomar M, Colquhoun SM, Cooper C, Cooper LT, Cortinovis M, Cowie BC, Crump JA, Damase-Derry J, Danawi H, Dandona R, Daoud F, Darby SC, Dargan PI, Das Neves J, Davey G, Davis AC, Davitoiu DV, De Castro EF, De Jager P, De Leo D, Degenhardt L, Delavalette RP, Deribe K, Deribew A, Dharmaratne SD, Dhillon PK, Diaz-Torné C, Ding EL, Dos Santos KPB, Dossou D, Driscoll TR, Duan L, Dubey M, Duncan BB, Ellenbogen RG, Elligsen CL, Elrizar I, Endries AP, Ermakov SP, Ehsreti B, Esteghamati A, Estep K, Faghihmuos IDA, Fahimi S, Faraon EJA, Farid TA, Farinha CSE, Faro A, Farvid MS, Farzadfar F, Feingel LA, Fereshtehnejad S-M, Fernandes JG, Fernandes JC, Fischer F, Fitchett JRA, Flaxman A, Foign F, Fowkes FGR, Franca EB, Franklin RC, Friedman J, Frostad J, Fürst T, Futran ND, Gall GL, Gambhisdze K, Gankrelidze A, Garguly P, Gankpe FG, Gebre T, Gebrehiwot TT, Gebremedhin AT, Gebru AA, Geleijne JM, Gessner BD, Ghoshal AG, Gilney KB, Gillum RF, Gilmour S, Giref AZ, Girou M, Gishu MD, Giussani G, Glaser E, Godwin WW, Gomez-Dantes H, Gona P, Goodridge A, Gopalani SV, Gosselin TA, Gotay CC, Goto A, Gouda HN, Greaves F, Gugnani H, Gupta R, Gupta R, Gupta V, Gutiérrez RA, Hafezi-Nejad N, Halde D, Hailu AD, Hailu GB, Halasa YA, Hamadeh RR, Hamid S, Hancock J, Hanafal AJ, Hankey GJ, Hao Y, Harb HL, Harikrishnan S, Haro JM, Havmoeller R, Heckbert SR, Heredia-Pi IB, Heydarpour P,
Tavakkoli M, Taye B, Taylor HR, Te Ao BJ, Tedla BA, Tefera WM, Ten Have M, Terkawi AS, Tesfay FH, Tessema GA, Thomson AJ, Thorne-Lyman AL, Thrift AG, Thurston GD, Tillmann T, Tirschwell DL, Tonelli M, Topor-Madry R, Topouzis F, Towbin JA, Traebert J, Tran BX, Truelsen T, Trujillo U, Tura AK, Tuzcu EM, Uchendu US, Ukwaja KN, Undurraga EA, Uthman OA, Van Dingenen R, Van Donkelaar A, Vasankari T, Vasconcelos AMN, Venketasubramanian N, Vidavalur R, Vijayakumar L, Villalpando S, Violante FS, Vlassov VV, Wagner JA, Wagner GR, Wallin MT, Wang L, Watkins DA, Weichenthal S, Weiderpass E, Weintraub RG, Werdecker A, Westerman R, White RA, Wijsonge CS, Wilkerson JD, Williams HC, Woldeyohannes SM, Wolfe CDA, Won S, Wong JQ, Woolf AD, Xavier D, Xiao Q, Xu G, Yakob B, Yamey GD, Yano Y, Younis MZ, Yu S, Zaidi Z, Zaki MES, Zannad F, Zavala DE, Zebh H, Zeleke BM, Zhang H, Zodpey S, Zonies D, Zuhlke LJ, Vos T, Lopez AD, Murray CJL. 2016. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet 388(10053):1459–1544 DOI 10.1016/S0140-6736(16)31012-1.

Wisneski KJ, Johnson MJ. 2007. Quantifying kinematics of purposeful movements to real, imagined, or absent functional objects: Implications for modelling trajectories for robot-assisted ADL tasks. Journal of NeuroEngineering and Rehabilitation 4(1):7 DOI 10.1186/1743-0003-4-7.