Robotic assessment of wrist and arm proprioception in healthy and stroke populations

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**NANYANG
TECHNOLOGICAL
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SINGAPORE

**ROBOTIC ASSESSMENT OF WRIST AND
ARM PROPRIOCEPTION IN HEALTHY AND
STROKE POPULATIONS**

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2018

ROBOTIC ASSESSMENT OF WRIST AND ARM PROPRIOCEPTION IN HEALTHY AND STROKE POPULATIONS

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Abstract

Proprioception is defined as the ability to know the position of the body in time and space exploiting the information arising from the periphery. It has long been recognized that impaired proprioception may severely affect the control of voluntary movements. However, the impact of these impairments on motor functions has been difficult to elucidate for two reasons: the qualitative nature of available clinical tests and the lack of instrumentation to accurately manipulate human limbs to measure proprioceptive performance. The recent advent of robotic interfaces designed for rehabilitation provides potential tools to quantitatively evaluate proprioceptive function. Up to this point, robotic devices have focused on testing single degree-of-freedom (DoF) joints such as the elbow, or were only capable of displacing or moving a joint in a single plane. The devices used to test multi-joint proprioception have a high level of complexity that require trained specialists to be implemented in clinics and can be cost prohibitive. Motivated by the lack of quantitative data on wrist proprioception and the lack of simple and cost-effective robotic protocols for assessment of arm proprioception, this thesis proposes quantitative tests which employ a 3 DoF wrist device and a low-cost planar robot. These robotic devices have first been used to evaluate the sensitivity and reliability of different robotic proprioceptive assessments in healthy individuals. The methodologies include a psychometric task in which participants are asked to discriminate two different positions while feedback is limited to proprioception, the joint position matching (JPM) task, in which participants actively match a predefined target and a revised version of the JPM task designed to overcome the limitations associated to motor impairments often present as a result of brain damage. These studies demonstrate that the quantitative metrics are sensitive and reliable over repeated testing and suitable for proprioceptive evaluation of intact joints. The effect of handedness, available feedback and external forces on proprioceptive measures has been analyzed, as well as the role assignment in the processing of sensory feedback during bimanual tasks and bimanual proprioception. No evidence of proprioceptive dominance was found, while there was a decline in performance when matching a target configuration which is visually and kinesthetically presented. Accuracy and precision in target matching do not change significantly as a function of an external load, while proprioceptive acuity was superior and more consistent during unimanual tasks compared to the bimanual case. Finally, the clinical applicability and validity of the robotic assessment of proprioception was evaluated. The methodology was employed to quantitatively assess deficits in acute, sub-acute and chronic patients. The test was found to be inherently simple such that all participants, regardless of motor impairment level, could complete it in less than 10 minutes. Further, the method provides quantitative metrics able to detect changes in proprioceptive status in clinical settings.

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Related published work

The work presented in this thesis is published in the following papers:

- **Contu, S.**, Hussain, A., Kager, S., Budhota, A., Vishwanath, D. A., Kuah, C. W., ... & Campolo, D., Proprioceptive assessment in clinical settings: evaluation of joint position sense in upper limb post-stroke using a robotic manipulator, *PLOS ONE*, 2017
- Marini, F., **Contu, S.**, Antuvan, C.W., Morasso, P., & Masia, L., The Influence of External Forces on Wrist Proprioception, *Frontiers in Human Neuroscience*, 2017
- **Contu, S.**, Hughes, C., & Masia, L., The role of visual and haptic feedback during dynamically coupled bimanual manipulation, *IEEE Transactions on Haptics*, 2015
- Cappello, L., Elangovan, N., **Contu, S.**, Khosravani, S., Konczak, J., & Masia, L., Robot-aided assessment of wrist proprioception, *Frontiers in Human Neuroscience*, 2014
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- **Contu, S.**, Marini, F., Cappello, L., & Masia, L., Does wrist proprioceptive acuity follow Weber's law?, *Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 2016
- **Contu, S.**, Hussain, A., Masia, L., & Campolo, D., A preliminary study for quantitative assessment of upper limb proprioception, *Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 2016
- Marini, F., **Contu, S.**, Hughes, C., Morasso, P., & Masia, L., Robotic assessment of manual asymmetries in unimanual and bimanual wrist joint position sense, *International Conference on Biomedical Robotics and Biomechatronics*, 2016

- **Contu, S.**, Hughes, C., & Masia, L., Influence of visual information on bimanual haptic manipulation, *14th IEEE/RAS-EMBS International Conference on Rehabilitation Robotics*, 2015
- **Contu, S.**, Cappello, L., & Masia, L., Preliminary analysis of non-dominant wrist proprioceptive acuity and asymmetry between upper limbs, *37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 2015
- Cappello, L., **Contu, S.**, & Masia, L., Wrist proprioceptive acuity: a complete robot-aided assessment, *37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 2015

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Chapter 1

Introduction

1.1 Proprioception in sensorimotor control

The sensorimotor system is a subcomponent of the motor control system which includes the sensory, motor, and central integration and processing components necessary to internally stabilize the body. Given the variety of tasks humans deal with in everyday life, these components must be flexible, adaptable, and should complement both static and dynamic components. Static components refer to ligaments, joint capsules, cartilages, and bones, while dynamic components relate to two kinds of neuromotor control over the muscles crossing the joint [1]. Feedback control refers to the adaptation or corrective mechanism in response to external changes during task execution detected by the sensory system. In contrast, feedforward control refers to motor planning and therefore anticipatory behaviour occurring before the sensory detection of impending events or stimuli.

Shadmehr and Krakauer [2] proposed a computational neuroanatomy of the motor system based on the mathematical approach previously presented by Todorov and Jordan [3] which links expected motor costs and rewards to the predicted and actual sensory feedback to generate the motor commands which maximize performance metrics. In the framework proposed, the basal ganglia have the role of providing the costs associated to the motor commands as well as the rewards from the predicted sensory states. The cerebellum predicts the effect of the motor commands on proprioceptive and visual feedback. These prediction are then compared to the the actual sensory feedback by the parietal cortex, which takes the role of providing

the current proprioceptive and visual states. According to the motor costs and the rewards of the proprioceptive and visual states, the premotor in conjunction with the primary motor cortex choose the gains to apply to the sensory states to obtain the motor commands according to the internal belief about states [2].

The combined inputs from three sensory systems, i.e. visual, vestibular and somatosensory systems, are important for both feedback and feedforward operations for motor control [4]. The somatosensory system, in particular, is comprised of sensory receptors and neurons in the periphery of the body, the spinal cord and the brain. Different sensory receptors are distributed in the periphery for the detection of different stimuli. These receptors are classified into four major types: nociceptors (pain), chemoreceptors (chemical characteristics), thermoreceptors (temperature), and mechanoreceptors (tactile sensation). Accordingly, somatosensory information are used to sense temperature, pain, tactile information such as touch, pressure, etc, and *proprioception* [5].

1.1.1 Definition and components

Based on the early descriptions by Sherrington [6], proprioception is defined as the ability to know the position of the body in time and space exploiting the information arising from the periphery. Submodalities of proprioception are joint position sense (posture), kinesthesia (active and passive motion), and sense of tension or force [7].

Proprioceptive information from a variety of mechanoreceptors is integrated for motor control. Mechanoreceptors are specialized sensory receptors that transduce mechanical pressure or distortion into neural signals. The mechanoreceptors responsible for proprioceptive information are located in the muscular, tendinous and joint (ligamentous and capsular) tissues. Mechanoreceptors in the cutaneous tissues are considered to be supplementary sources of proprioception. To distinguish the mechanoreceptors in the musculoskeletal system which provide information about mechanical forces arising from the body itself, the term proprioceptors, which means “receptors for self”, is also used [8]. These are classified as rapidly adapting (phasic) or slowly adapting (tonic) receptors respectively when they respond maximally but briefly to stimuli or when they keep firing when the stimulus is maintained. Therefore, rapidly adapting receptors and slowly adapting receptors can provide information about both the dynamic and static aspects of a stimulus. Receptors are

also defined as low-threshold (or high-sensitivity) when they fire even in presence of weak mechanical stimulation.

Mechanoreceptors present in the musculotendinous tissue are the Golgi tendon organs and muscle spindles. Golgi tendon organs are encapsulated afferent nerve endings found within the intersection of muscles and tendons. They respond to low stimuli amplitude and have high dynamic sensitivity in signaling active muscle tension in response of muscle contraction, while are relatively insensitive to passive stretch [9]. Muscle spindles are found in all but a few skeletal muscles. They consist of intrafusal fibers, which are specialized muscle fibers present in a parallel arrangement among the ordinary fibers, and are surrounded by a capsule of connective tissue. According to the type of intrafusal fibers, they can be sensitive to changes in muscle length or to its rate of change. Muscle spindles can send proprioceptive information centrally at all muscle lengths during movements and postural adjustments [10].

Four types of receptors are distributed in the ligamentous and capsular tissues: Ruffini endings, Pacinian corpuscles, Golgi tendon organ-like endings, and free nerve endings. Ruffini endings are unencapsulated receptors which constantly react to loadings along the axial direction and tensile strain in the ligament during joint motion. They have low-threshold, slow-adapting characteristics. They do not react to perpendicular compressive joint forces, indicating their greater sensitivity in response to joint position and rotation compared to pressure [11]. The Pacinian corpuscles are rapidly adapting, high-threshold encapsulated receptors which respond to changes in joint velocity and are able to sense mechanical disturbances at a distance. They have high sensitivity to compression but not tensile forces, and they can sense sudden perturbations occurring at the joint, signalling harmful joint motions [12]. The Golgi-like endings respond to tensile strain in the ligament when the joint angle is reaching the anatomical limits, while are silent in the immobile joint [13]. Free nerve endings are unencapsulated dendrites of sensory neurons [14]. The distribution of mechanoreceptors in the shoulder, elbow and wrist joint has been analyzed in histological studies and can be found respectively in [15–17].

The input received from the proprioceptors are initially integrated at the level of the spinal cord, and sensory information that enters the ascending tracts is modulated by the supraspinal central nervous system (CNS) regions. The signals are

transmitted through the dorsal lateral tracts in the posterior region of the spinal cord to the parietal lobe in the somatosensory cortex. From the spinocerebellar tracts, a faster transmission conveys the information to different areas of the cerebellum, in which it is believed that the signals are integrated with afferent and descending signals.

1.1.2 Importance of proprioception

Sensory feedback generally comes from partially redundant afferent information from the somatosensory, visual, vestibular systems, which have different accuracy and are conveyed to the CNS at different speed. Among the sensory information, proprioception is used in motor control for two main purposes: to react to changes in the external environment and to plan and update the internally generated motor commands [18]. Proprioception is crucial for movement execution. Indeed, it modifies the feedforward commands obtained from the visual system, especially in situations in which visual attention does not note unexpected perturbations. With regards to reaching motor tasks, the target position is usually visually acquired, while we can sense the current position of our arm via both vision and proprioception. Experiments with animal [19] and human subjects [20] with parietal cortex damage revealed that the lesions in the superior parietal lobule cause mis-reaching of targets defined in proprioceptive coordinates. The lesions, however, did not affect the capability to reach target positions when vision of the arm could have provided a sense of limb's position [2].

Proprioception also allows the motor control system to determine how much tension in different muscles is necessary for a particular movement considering the effect of the movement of one joint on the others (intersegmental dynamics). Interaction torques, normally controlled through feedforward mechanisms, are compensated by motor commands generated by an internal model of limb dynamics updated by proprioceptive information. Proprioceptive impairments, indeed, cause difficulties in performing multijoint unconstrained movements due to the failure to adapt motor commands to the biomechanical properties of the limb, so that the interaction torques at the joints and forces transferred between limbs are not compensated [21]. The timing of biceps and triceps activity during elbow rotation related to changes in interaction torques present in healthy subjects is replaced with their cocontraction

in deafferented patients [22]. As a consequence, the accuracy of movements which involve several joints aimed at visual targets is often impaired after proprioceptive losses.

1.2 Proprioceptive impairments after stroke

Stroke is one of the principal causes of death and permanent disability in developed countries [23]. Impaired motor functions are common consequences of this neurological condition, including the loss or limitation of muscle control and mobility [24]. Upper limb motor impairments severely impact the ability to perform daily activities, such as feeding and dressing, and reduce the quality of life [25].

In neurological conditions like stroke, somatosensory deficits accentuate the motor impairments and thereby functional loss, more so in the fine motor tasks of the hand, that require sensorimotor integration [26]. A clear example of the importance of somatosensation is provided by a pioneering study by Rothwell in the early 80s, who studied manual motor function in a deafferented man with a severe sensory loss. The author found that the subject could perform trained complex tasks even with sensory loss, but could not translate this skill to other similar activities due to limited learning - a consequence of lack of sensory feedback [27]. More recent studies have also shown how defective somatosensory functionality is related to lower functional ability and longer length of hospitalization [28, 29]. Hence, a clear understanding of somatosensory loss is critical for identification of individuals specific therapy regimes.

Somatosensory dysfunction can affect tactile sensation, temperature discrimination and proprioception [30, 31]. As discussed in the previous section, proprioception is a critical component for motor control. Stroke patients presenting defective proprioceptive abilities may present difficulties in the estimation of their limbs position and maintaining them in a steady posture in absence of vision [27], resulting in negative implications for safety [32]. Their grip force modulation is affected due to faults in the estimation of sensory prediction errors necessary for on-line corrections during object manipulation [33]. Further, defective proprioception hinders the generation of smooth and coordinated movements [34], and leads to difficulties in learning novel movements and in improving the quality of movement over time with

functional repetitions [35].

Hemiparesis as a result of stroke alters the base of support and changes the biomechanical configuration of the body which requires a postural adaptation. Loss of proprioception can affect the postural adaptation and worsen rehabilitation outcome [36]. Further, patients with impaired proprioception fail to compensate for interaction torques at the joint level, which results in misdirected reaching arm movements [37].

Finally, proprioception has shown a strong correlation with motor recovery of the hemiplegic arm [38–40], and patients presenting sensory and motor impairment have a worse prognosis in comparison of patients with manifest loss of motor function [41].

1.3 Clinical assessments

Conventional scales for the assessment of proprioception are generally rudimentary and are used only for a basic screening of participants for adopting therapy regimes. Despite its importance, research into somatosensory impairment and recovery is limited. Moreover, differences in populations, somatosensory modalities and body areas evaluated have resulted in contrasting estimates of somatosensory impairments extent [30].

Despite the lack of standardized methods to assess sensory functions, most of the therapists routinely perform somatosensory assessments [29] using ad hoc instruments that provide only qualitative measure, such as light touch tested by mean of cotton wool, the examiners finger-tip or a feather [42]. The resulting non-standardized metrics have been recognized as insensitive [43, 44] or have been analyzed inappropriately [45]. Few standardized sensory assessments have been proposed, which, however, consist in qualitative screening tool rather than comprehensive assessments of somatosensory performance as their score can distinguish between “absent”, “impaired” or “normal” functions [41]. These clinical assessments of somatosensory perception include the Fugl-Meyer Sensory Scale, the Nottingham Sensory Assessment (NSA) and the Rivermead Assessment of Somatosensory Performance (RASP) test.

The Fugl-Meyer Sensory Scale is often used in clinical practice to measure both motor and sensory abilities, i.e. light touch and proprioception, in stroke patients

[46]. Studies have found an excellent inter-rater reliability for the sensory scale of the Fugl-Meyer test [47], but also significant ceiling effect [48].

The NSA test consists of three subtests evaluating tactile sensation (light touch, temperature, pinprick pressure, tactile localization, bilateral simultaneous touch), kinesthetic sensations (recognition of movement onset, direction of movement, joint position sense) of different parts of the body and stereognosis (identification of object such as coins, pencils, cups etc.) [49]. A modified version of the NSA, called the Erasmus MC modified version (Em-NSA), was proposed in 2006. It includes light touch, pressure, pinprick, sharp/blunt discrimination, two-point discrimination, and proprioception test and still provides results in an ordinal scale [50]. A study proved its good intra- and inter-rater reliability [48].

The RASP test is considered a more reliable test that covers many body parts and a wide representative range of clinical analyses which are important for somatosensory assessments such as sharp/dull discrimination, surface pressure touch, surface localization, sensory extinction, two-point discrimination, temperature discrimination, proprioceptive movement and direction [51].

The clinical scales have different nature and produce outcomes that still lack the reliability and sensitivity necessary to accurately monitor proprioceptive status. For example, Tyson and colleagues performed a proprioceptive assessment by mean of the RASP test, which resulted in the identification of deficits in the 27% of 93 acute stroke patients screened, with no difference between arm and leg proprioception [31]. In a subsequent study with 102 patients, the authors found a high redundancy between elbow, wrist, thumb, ankle and big toe proprioception and suggested that only the palm of the hand, thumb, dorsum of the foot, and the ankle can be tested to reduce administration time of the RASP test [52]. In another study by Connel et al., however, the authors found that among 70 patients screened using the NSA, impairments ranged from the 34% at the ankle to 63% at the shoulder [41]. Interestingly, while Tyson and colleagues found a higher ratio for tactile deficits than proprioceptive ones, the group of Connel found that proprioception was more frequently impaired compared to tactile sensations. In a recent study by Meyer et al., proprioception of 122 patients within 6 months after stroke was tested with the revised version of the NSA, the Erasmus-modified NSA (Em-NSA) [50] and the thumb finding test [53], in which patients were asked to grab the impaired thumb placed in

a target position by the experimenter. Impairments evaluated by the Em-NSA were diagnosed in 23% of the study population, whereas the thumb finding test identified deficits in the 54% of the patients screened [54].

Correlation between sensorimotor and functional scales have also been evaluated. Tyson and colleagues found a correlation between sensory and functional modalities, and recommended to measure both in order to measure sensory recovery [31]. Welmer et al. screened 66 patients at one-week post-stroke and in two follow up sessions at 3 months and 18 months. While light touch and positioning of the thumb moderately correlate with hand functions in acute and subacute stroke, the correlation was weak in the chronic stage, possible as a result of compensatory strategies acquired with time which exploited vision [55]. Similarly, 20 chronic patients showed impairments of all sensory modalities of the arm and moderate to severe motor deficits, and no correlations between the results of the FMA motor test for the wrist and hand and the corresponding NSA scores [56]. Somatosensory deficits in subacute patients poststroke have been found to be correlated to the motor outcome, especially in patients with visuospatial neglect compared with patients without neglect [54].

Up to date, clinical scales for assessment of proprioception do not provide a clear distinction between different subcomponents of proprioception, i.e. the perception of joint position, active and passive movement (kinesthesia) and force and effort [57].

Joint position sense (JPS) is one of the most widely considered indicators for the assessment of proprioception, as accurate JPS information is essential for movement planning and postural control. Determining the integrity of the joint position submodality involves the quantification of the accuracy of joint-angle replication and is usually assessed through active or passive matching of a target joint position. In the active matching task, the subject is required to voluntarily move a joint or a limb to a pre-defined target position. Contrarily, in the passive matching task, the participant's limb is moved to a target position, returned to the initial position and then moved again until the subject recognizes that the previously determined target position has been matched. Objective quantification of JPS is possible through technology such as goniometers, electrogoniometers, isokinetic dynamometers, electromagnetic tracking devices, custom-made jigs and inclinometers [7, 58, 59].

An alternative approach to assess the JPS status is to obtain the psychophys-

ical thresholds. These threshold hunting methods yield two types of thresholds: a detection threshold and a discrimination threshold [60]. The detection threshold reflects the smallest change in position of a joint or a limb that can be perceived by an individual. The discrimination threshold, on the other hand, is the minimum difference between joint or limb positions that can be perceived by an individual, and it is measured as the just noticeable difference (JND). The JND is based on the discrimination between two different stimuli and consists in the measure of the minimum perceivable difference in stimulus position that is necessary to be discriminated correctly by roughly 75% of the subjects responses: such indicator provides the quantification of proprioceptive acuity or minimum proprioceptive threshold perceived by the subject. The detection threshold is considered a measure of the sensitivity while the discrimination threshold represents a measure of acuity. The accuracy of proprioceptive thresholds estimation is still an open debate and it is strongly influenced by inter-trial variability in human-operated assessments and absence of high-resolution clinical scales. Assessments performed with the help of robotic devices can overcome the limitations that affect the quantification of JPS and proprioceptive thresholds.

1.4 Robotic technology for proprioceptive assessment

Conventional physiotherapy allows improvements in motor functions superior to the achievable with natural recovery alone, even in the chronic stage of recovery. Accordingly, the high demand for neurorehabilitation resulted in an increased interest for technology-assisted systems aiming at reducing the therapist’s workload while promoting recovery at an affordable cost [61–63]. Robotic technology for rehabilitation has the capacities to potentially improve the efficacy of rehabilitation protocols, providing an intensity and duration of training in the clinic or at home that would be cost-prohibitive for a traditional patient-human therapist interaction. Further, robotic technology allows the development of novel paradigms to complement conventional neurological rehabilitation: it can provide a task-specific and interactive environment to enhance motor learning of the impaired limbs. As a result, several robotic solutions have been developed in the last couple of decades [64–67]. To

date, clinical studies with these setups have shown that robot-assisted therapy of the upper-extremity is at least as effective as conventional rehabilitation therapy in reducing motor impairments [63, 68, 69].

Robotic devices designed to promote sensorimotor learning have recently been proposed. Sanguinetti proposed robotic rehabilitation tasks that explicitly target proprioceptive deficits where stroke patients were requested to perform part of the experiment with no vision of their limb and with no visual feedback from the robot while executing a point to point reaching task [70]. Subjects could not visually estimate limb positions, but they needed to rely on the force provided by the robot and on the proprioceptive feedback to complete the task; results showed a significant improvement over the training sessions, and the final performance was comparable to those of another age-matched group exercising in normal conditions with visual feedback. A successive work demonstrated that also severely impaired subjects may report significant benefits after proprioception-enhancing therapy [71]. Evidence of subjects' recovery was assessed by kinematic analysis, where smoother and straighter final trajectories were considered improvements in the sensorimotor performance. Despite improvements in proprioception were tangible, the proposed work does not include a dedicated method to assess proprioceptive acuity. Assessment and training of proprioception still lack a standardized method based on specific devices able to quantify and deliver therapy for patients suffering from sensory deficits. Since proprioceptive training has been shown to improve the efficiency of rehabilitation in patients with sensorimotor impairments, proprioception should be assessed before and during the rehabilitation program.

In conjunction with sensorimotor training, robotic devices can potentially provide objective and reliable means for monitoring the patient's progress [63]. However, the role of technology as an assessment tool has been explored less thoroughly, and a limited amount of work has been done in evaluating the somatosensory integrity and changes related to the motor training. Quantitative assessment routines have been proposed in recent years using technological solutions, which quantify proprioceptive deficits based on movement detection [72, 73], discrimination [33, 74–76] and position matching [73, 77–82].

In the context of rehabilitation, a planar robotic manipulandum was used to obtain motion sense thresholds of the arm of both healthy and stroke patients [74, 75].

A planar robot was also proposed by Mrotek to apply force perturbations which produced displacements of the handle to test when participants could detect arm motions [72]. The planar robot InMotion2 (clinical version of the MIT-Manus) was used to test the ability of healthy participants to discriminate the direction of forces deflecting their reaching movements [76]

An exoskeleton robot called FINGER for the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints was used to test the precision of healthy participants in determining the fingers overlapping and the onset of a finger movement [73]. The Robotic Sensory Trainer proposed by Lamercy was used to evaluate JPS of the metacarpophalangeal joint [33]. This system provided displacement, vibration, and pressure stimuli to the users finger for the assessment and therapy of hand sensory functions. Bimanual robotic devices were proposed for determining JPS thresholds in stroke subjects by the groups of Squeri [80] and Dukelow [82]. The manipulanda, called respectively Braccio di Ferro 2 (BdF2, Celin srl, La Spezia, Italy) and KIN-ARM (BKIN Technologies, Kingston, ON), were used in the joint position matching paradigm to passively place one arm into a target position that the subjects actively matched with the other arm [77–82].

1.5 Proposed devices and methodology

Robotic rehabilitation has been successfully employed to reduce motor impairments at the joints exercised during the routines, with improvements that, however, are not generalized to the unexercised muscle groups. Arm rehabilitation has usually no effects at the wrist and fingers, which require joint and task specific intense, active and repetitive movements. The wrist joint is crucial for activities of daily living, as it allows the hand to take the orientation necessary for the required task or object manipulation. Although wrist motor rehabilitation devices exist, most lack data demonstrating their clinical effectiveness and none have focused on both diagnostic and therapeutic functions for proprioceptive deficits that affect the degraded fine-motor control after stroke.

Up to this point, most robotic devices have focused on testing single DoF joints such as the elbow, or were only capable of displacing or moving a joint in a single plane (i.e. dorsiflexion/plantarflexion of the ankle). This constraint restricts either

the types of joints that can be investigated, or it provides only partial information on the proprioceptive status of a joint. However, it is clinically relevant to examine the proprioceptive function of all degree of freedoms (DoFs) of a given joint or limb system. Finally, there is limited amount of literature on wrist proprioception due to its complexity: several small bones interconnected with multiple tendons and ligaments, no pure axis of rotation, movements and rotations in three DoFs and very limited functional range of motion compared to other joints. On the other hand, the devices used to test arm proprioception have a high level of complexity that require trained specialists to be implemented in clinics and can be cost prohibitive. In this thesis, two robotic devices are proposed to solve these problems: a 3-DoF wrist device called Wrist Robot and a low-cost planar robot called H-Man.

Among the different paradigms to test proprioception, this thesis reports the validity and feasibility of different approaches which employed robotic devices: Chapter 2 presents the Joint Position Matching (JPM) task and the 2-alternative-forced-choice (2AFC) discrimination paradigm, while Chapter 5 describes a refined JPM task which takes into consideration the practical limitations of the first two tests in clinical environments.

The effect of several factors has also been tested. The factors included handedness, target presentation modality and external forces (Chapter 3). After the evaluation of the roles of the two hands during bimanual tasks, we also compared unimanual and bimanual proprioceptive performance, as reported in Chapter 4. Further, we estimated proprioceptive functions of both arm and wrist of healthy subjects in different age groups and analyzed the effect of aging on proprioception, as described in Chapter 5. Finally, the refined JPM has been applied to the chronic and acute and sub-acute stroke population to detect proprioceptive impairments.

1.5.1 Wrist Robot

All the experiments evaluating wrist proprioception employed the Wrist Robot, the 3-DoF manipulandum shown in Figure 1.1A. It is fully backdrivable and allows almost full anatomical range of motion for the human wrist (flexion/extension, FE: 65/70°, abduction/adduction, AA: 19/30° and pronation/supination, PS: 90/90°) along the three DoFs (FE: $\pm 72^\circ$, AA: 45/27° and PS: $\pm 80^\circ$), shown in Figure 1.1B. It is provided with four Maxon brushless motors (one EC-45 flat 70 W direct drive

Figure 1.1: (A) The Wrist robot, the three-DoF manipulator used for the assessment of proprioception; (B) Movements in the 3 DoFs of the wrist with reference to an initial neutral position of the robot; (C) Bimanual setup composed by two identical Wrist robots.

for FE, two ECI-40 70 W with 14:1 gearhead for AA and one ECI-40 70 W with 3.7:1 gearhead for PS) and it is able to display enough torque to move passively the joint. The maximum continuous torque levels provided by the motors are 1.53 Nm for FE, 1.63 Nm for AA, and 2.77 Nm for PS.

The robot can provide an accurate haptic rendering and compensates for the weight and inertia of the device. Angular rotations of the three DoFs were acquired by means of 4000 quadrature-counts/revolution incremental encoders. The mechanical transparency of the device was enhanced by a control algorithm, for inertia and gravity compensation, intended to reduce force and effort during the task and to avoid involvement of muscles except those crucial for the task. Furthermore, the handle of the device was carefully designed in order to allow anatomical grasp and minimise stretching of the fingers that may lead to exaggerated activation of flexor/extensor muscles during the active phase of the matching task. The control architecture is based on three loops: 1) an inner loop, running at 1 kHz in the motor servos; 2) an intermediate loop running at 1 kHz on a real-time processor that updates the current reference of each motor; 3) an external loop running at 100 Hz for the user interface. The gain parameters of the PID controller running inside the Maxon EPOS2 motor drivers were finely adjusted in order to have very smooth movements necessary for the tests of the present paper. The PC is equipped with a PCI-express Hardware-in-the-Loop (HIL) control board (Quanser Quarc QPIDE) which provides real-time capability, of which we use the following channels: a) eight 16 bit D/A channels for commanding the reference values of the motor currents; b) eight 20 MHz encoder inputs for receiving the pulses from the digital encoders. The

software environment was based on Matlab Simulink. Given the high performances of the control software and of the HIL control board, a bimanual workstation has been implemented, where two subjects per time can take part to the experiments (without interfering to each other) or a subject can perform bimanual tasks. The apparatus includes a screen, placed approximately 50 cm away from the subject, in order to provide visual feedback relevant to the tasks when required (Figure 1.1C).

1.5.2 H-Man

H-Man, a planar robotic manipulandum designed for the rehabilitation and training of upper-limb sensorimotor functions, was used in the experiments [83]. It is actuated by two motors in a differential configuration that drive two perpendicular linear sliders upon which a handle is attached, as shown in Figure 1.2. The motors can provide forces of up to 30 N at the end-effector in any specified direction in the workspace. These forces are used to assist or resist the motion of the user. H-Man has a homogeneous behavior across its workspace and present low friction and low inertia. It is easy to control, lightweight (about 7 kg) and intrinsically safe.

The apparatus is integrated with a PC equipped with a real-time control unit, Quanser QPIDE, which acquires the signal from the encoders and commands the values of the motor torques through QUARC blocks in a Simulink model. The same model manages the communication via transmission control protocol (TCP/IP) between the real-time system and a visual interface designed in the Unity game engine. The visual outputs are displayed on a 20" computer monitor. The interaction with H-Man is simplified by a graphical user interface based on the MATLAB GUI-Guide

Figure 1.2: *H-Man, the planar robot designed for the rehabilitation and training of upper-limb motor functions employed as assessment tool for proprioceptive status.*

tool which allows the selection of multiple assessment tasks or training schemes for rehabilitation.

Chapter 2

Robotic assessment of wrist proprioception

As introduced in Chapter 1, robotic devices offer new tools to complement conventional stroke rehabilitation. They offer task-specific training that use interactive environments for high-intensity exercises that can be administered to the impaired limb in a repetitive way, as well as a quantifiable tool for assessing the patients' progress [63, 84]. The application of robotic technology to the study of the proprioceptive function and the therapeutic approach to recover from sensory deficits has only recently started to emerge.

In this chapter, the use of the Wrist robot as an assessment tool for wrist proprioceptive acuity is introduced. We report evidence supporting the validity of the proposed approaches in terms of sensitivity to distinguish between the different DoFs of the wrist and reliability between multiple tests. We also provide a full characterization of the proprioceptive acuity which generalizes the results providing a metric that is independent of the choice of stimuli chosen for the assessment. To this end, we first tested the hypothesis that accuracy of perception of the wrist position is constant across a wide range of stimuli amplitudes, as suggested by the Weber's Law. We then provide acuities for passive movements and the measured Weber's fraction for proprioception.

The results presented in this chapter can be found in [85–87].

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37th Annual International Conference of the IEEE, 2015.

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2.1 Evaluation of proprioception through Joint Position Matching

The importance of proprioception in the field of rehabilitation has recently emerged due to the finding that limb position sense, which is impaired in one-third to half of stroke patients [88,89], has a prognostic significance in motor recovery of the hemiplegic arm [39,53,90]. The quality of motor control of a variety of movements, such as aiming, reaching and tracking movements is affected by the incorrect perception of joint position [30,91].

Given the importance of proprioception in clinical practice, accurate methods for its assessment and characterization are needed. One to one (patient and therapist) approaches have been designed to evaluate joint position sense in stroke subjects [92,93], but they rely on the manual repositioning of the affected limb by the examiner. Specifically, the quantification of joint angle perception consists in the evaluation of the accuracy and precision of the active replication of angular displacements [94]. In this test, the subject’s joint is moved by the experimenter to a target position and returned to the initial position, after which the active movement starts with the goal of replicating the experienced position. As introduced in Chapter 1, quantitative measures for JPS have been obtained in terms of accuracy and precision by using simple goniometers, electrogoniometers, isokinetic dynamometers, electromagnetic tracking devices, custom-made jigs and inclinometers. Also a photograph or a video taken during the experiment has been analyzed for the quantification of joint position sense [95]. Although JPS is one of the most widely used measures of proprioception found in the literature, few studies have applied this method to the wrist, and so far, data are scarce [96].

Despite the use of some quantitative assessment tools, differences are present

when different observers measure joint rotation. The study from Solgaard and colleague, for instance, reported inter-rater variation between 6 to 10° when using a simple goniometer to measure wrist rotations under standardized conditions [97]. Further, these devices have different reliabilities as documented by the study from Goodwin and colleagues, who compared three different goniometers and found superior reliability for electrogoniometer compared to either the universal and fluid goniometer [98].

Robotic manipulanda are well suited to perform the proprioceptive assessment of the human joints thanks to features such as high encoder resolution, elevate positioning accuracy and wide torque range. The following sections report the evaluation of the feasibility of using the Wrist robot (presented in Section 1.5.1) to determine proprioceptive accuracy and precision for the different DoFs of the wrist. We report data validity in terms of the capability of the system to produce measures of proprioception in line with previously published results.

2.1.1 Participants and procedure

Fourteen right-handed participants (mean age $\pm$ SD: 26.9 ± 3.86 years; 8 males) participated in the study. All participants were right-handed as assessed using the Edinburgh Handedness Inventory [99], and did not have any known neuromuscular disorder. The experiments were conducted in accordance with local ethical guidelines and conformed to the Declaration of Helsinki.

Participants underwent the ipsilateral joint position matching task (JPM) [100] in the FE and AA DoFs of the dominant wrist. They sat on a height adjustable chair in front of the robotic device and placed their right forearm on the rigid cast of the robot. They grasped the handle which was initially placed in a neutral configuration (0° in FE and 0° in AA) and were blindfolded. After ensuring the best alignment between the axes of the robotic system and the wrist’s anatomical ones, the subjects’ forearm was firmly strapped to avoid any shift in wrist position during the test and achieve repeatability of the subject’s wrist position.

As shown in Figure 2.1, during the *Criterion movement*, the wrist was moved by the robot to the target position so that the participant could memorize the position via proprioceptive feedback. An auditory cue (high-frequency beep) marked the start of the criterion movement, in which the wrist was moved by the robot to match

Figure 2.1: *Experimental protocol.* An auditory cue marks the beginning of the *passive criterion movement* on the target position. After a 3-second dwell time, the joint is passively returned to the initial position. After 2 seconds, an auditory cue indicates the beginning of the *matching movement*, in which participants actively reproduce the joint configuration previously experienced without any interference from the robot. When the end effector speed is below a $2^\circ/\text{s}$ for more than 2 seconds, the robot brings the wrist to the starting position for the following trial.

the target position (32° for FE and 16° for AA). After a hold time of three seconds [58,101], the wrist was passively returned to the initial position to start the *matching movement* concurrently to a low-frequency auditory cue, after which participants actively reached the target position. During this phase, the robot did not deliver any force at the wrist joint [102]. The active matching phase was considered complete when the speed of the end effector was lower than $2^\circ/\text{s}$ for more than two seconds, after which the robot moved the wrist back to the neutral position. Participants were instructed to focus on the *criterion movement* end location ignoring the movement kinematic, and replicate such position as accurately as possible during the *matching movement* with a self-paced movement. Moreover, they did not receive any feedback about their performance to avoid recalibration of the following responses [102].

Participants performed 12 trials in each DoF, yielding a total of 24 trials. Trials across DoFs and conditions were presented in a pseudo-random fashion. The entire experiment lasted approximately 30 minutes.

2.1.2 Data analysis and results

Wrist proprioceptive acuity was measured from the active joint angle replication using two outcome measures: *Absolute Error* [34] and *Variability* [82].

The *Absolute error* is a measure of accuracy of proprioception, and is defined as the absolute difference between the target and the matched angle:

$$\text{Absolute Error} = \frac{\sum_{i=1}^N |\theta_T - \theta_i|}{N} \quad (2.1)$$

where θ_i is final position of the wrist on the i -trial and θ_T is the target position. The average error across N repetitions of the same target in each of the tested DoFs was considered for the statistical analysis, where $N = 12$.

The *Variability* is a measure of precision of the target estimation, reflecting the inter-trial repeatability (standard deviation) across the N repetitions:

$$\text{Variability} = \sqrt{\frac{\sum_{i=1}^N (\theta_i - \bar{\theta})^2}{N - 1}} \quad (2.2)$$

Differences in matching accuracy and repeatability across movements were tested with a repeated measure ANOVA, and statistical significance was set at $p < 0.05$. F -statistic and p values for the tests are reported to determine if the variance between the means of diverse populations are significantly different. F is based on the ratio of mean squares, the estimate of population variance that accounts for the degrees of freedom (number of observations in the data that can vary when estimating the statistic). The F -statistic is used to compute the p -value, which represents a measure of the strength of evidence against the null hypothesis that there is no significant difference between specified populations. For a more detailed explanation, the reader can refer to [103].

Mean metrics $\pm$ SD across subjects in the different movement directions are reported in Figure 2.2. Absolute errors were the highest for Extension movements ($4.52 \pm 2.21^\circ$), followed by Adduction ($3.69 \pm 1.68^\circ$), Flexion ($3.31 \pm 1.68^\circ$) and finally Abduction ($2.91 \pm 1.46^\circ$). The analysis, however, did not detect a significant main effect of movement direction on the Matching error, $F_{(3,39)} = 2.65$, $p = 0.06$. From the pairwise analysis we found the highest difference between errors in Extension and Abduction movements (1.61°), which however did not result significant ($p = 0.17$). Absolute errors were smaller for the AA DoF ($3.30 \pm 1.27^\circ$) compared to FE ($3.92 \pm 1.48^\circ$). The difference was not statistically significant, $F_{(1,13)} = 2.23$, $p = 0.16$.

Contrarily to the Absolute error, the analysis of Variability revealed a main effect of movement direction ($F_{(3,39)} = 5.72$, $p = 0.002$) and DoF ($F_{(1,13)} = 16.79$, $p = 0.001$), with higher variability in Extension ($3.75 \pm 1.45^\circ$) and Flexion ($3.00 \pm$

Figure 2.2: *Wrist proprioceptive acuity in terms of mean $\pm$ SD Matching error and Variability across subjects. Black bars refer to FE DoF, while white bars refer to AA.*

1.03°) compared to Adduction ($2.54 \pm 0.68^\circ$) and Abduction ($2.29 \pm 0.77^\circ$). Mean Variability in the DoFs analyzed showed a higher precision along the AA DoF ($2.41 \pm 0.64^\circ$) compared to FE ($3.38 \pm 0.75^\circ$).

2.2 Sensitivity of the JPM task

The proprioceptive acuity of the healthy dominant wrist has been obtained in terms of matching accuracy and precision. The data will serve as a baseline measure for future studies to differentiate proprioceptive accuracy in the wrist DoFs and to detect sensory impairments. The technology employed allowed to measure errors similar to the findings of a previous study which reported Absolute errors of $5.9^\circ \pm 3.5^\circ$ and variability of 4.6° [58].

Interestingly, we found an effect of movement direction, which is expected considering the neuroanatomy of the wrist. Mechanoreceptors in the ligaments primarily stressed during AA, such as dorsal radiocarpal, dorsal intercarpal and scapholunate interosseous ligaments, have a high density of mechanoreceptors. The ligaments involved in FE movements are instead the less innervated volar and volar-triquetral ligaments, which have a lower density of receptors [17, 104]. Furthermore, the acuity in the different DoFs correlates with the respective ranges of motion. During joint passive motion, capsular afferents respond only during movements close to the limit

of the range of motion, adding information to the signal continuously generated by the muscle spindles [1]. The AA DoF has the smallest ROM, and the stimuli, which have been chosen independently from the DoF evaluated, move the wrist closer to the extreme position allowed, in which the mechanoreceptors response is stronger, and thus enhances the ability to discriminate the two stimuli.

2.3 Just Noticeable Difference as a measure of proprioception

In order to test the awareness of the location of the joint in space, the JPM method is commonly used to measure the accuracy of joint-angle replication. Another possible approach consists in the assessment of the psychophysical thresholds: the detection threshold, which is the smallest perceivable change in position, and the discrimination threshold, which is the just noticeable difference (JND) between two perceived positions [60]. The detection threshold is considered a measure of the sensitivity while the discrimination threshold, or JND, represents a measure of acuity. The JND represents the smallest change in stimuli that can produce a noticeable variation in sensory experience, and, more formally, it is the minimum difference between two test parameters that is necessary in order for the difference to be discriminated correctly by 75% of the subjects responses.

The JND as a measure of proprioception acuity has been shown to provide a more precise and least variable measure compared to the accuracy of joint-angle replication [105]. In order to evaluate the JND for position discrimination, we run a unidirectional 2-alternative-forced-choice (2AFC) discrimination paradigm. In this test, two different stimuli are presented in each trial: the Standard stimulus, a stimulus of fixed value, and the Comparison stimulus, a variable amplitude stimulus greater than the Standard. The participant is asked to determine which, of the two stimuli, presented in random order, is the Comparison.

The discrimination threshold hunting paradigm requires an accurate and precise control of limb movement kinematics, which can be achieved by haptic technology and robotic systems. These are indeed able to passively move a limb in a highly controlled manner, and, as a consequence, have been recently introduced as tools for proprioceptive assessment, although mainly for testing single DoF joints such as the

elbow and were only capable of displacing or moving a joint in a single plane (i.e., dorsiflexion/plantarflexion of the ankle). This constraint restricts either the types of joints that can be investigated and provides partial information regarding the condition of joint proprioception. It is instead relevant, especially from the clinical point of view, to examine the proprioceptive status of all DoFs of a single joint or limb.

Based on the capability of the Wrist robot, we employed such system to accurately deliver in a repetitive way the position stimuli in the different anatomical planes of movement and consequently measure wrist proprioceptive acuity in terms of JND. We evaluated the feasibility of the approach and the validity of the proprioceptive discrimination thresholds and its sensitivity for detecting small differences in acuity in the different DoFs. Finally, we established the test-retest reliability of the protocol, which indicated that the approach provides reliable estimates of proprioceptive acuity over repeated testing.

2.3.1 Participants and assessment protocol

A total of seventeen subjects participated in the experiments. Eleven right-handed young adults (mean age $\pm$ SD: 26.4 $\pm$ 3.4 yrs.) volunteered to test their proprioceptive acuity in Flexion and Abduction of their wrist. Among these subjects, five were chosen to test the test-retest reliability of the system. Six participants (mean age $\pm$ SD: 27.7 $\pm$ 3.3 yrs.) were tested in Adduction, Extension, Pronation, and Supination. Prior to experimentation, the laterality index of each participant was tested with the Edinburgh Handedness Questionnaire [99], which confirmed that they were all right-handed. Only the dominant right hand was evaluated. The experimental sessions were performed using the same instrumentation in the Robotics Research Centre belonging to Nanyang Technological University in Singapore and School of Kinesiology of the University of Minnesota. All participants gave their informed consent prior to testing according to the ethical guidelines specified by the Institutional Review Board of the respective site of the testing.

Subjects sat on a height-adjustable chair beside the robot, with their dominant right arm resting on a rigid cast. The frontal plane of their body was aligned perpendicularly to the PS axis of the robot, and they were instructed to face forward during the whole duration of the experiment. Their elbow was bent at an angle of

Figure 2.3: (A) *Experimental session.* Participants wore ear muffs and opaque glasses to avoid external cues. (B) *Stimuli during a trial.* The Standard stimulus had a fixed amplitude of 15° , while the Comparison stimulus was variable but always larger than the Standard. (C) *Intensity, defined as stimulus difference between comparison and standard stimuli, presented across 100 trials for one participant.* Comparison stimulus rapidly decreased from 22° to $\sim 17^\circ$.

$\sim 90^\circ$, and their wrist joint was aligned with the functional axis of the robot, which was initially adducted of 10° from the neutral position to account for the anatomical limit of the workspace and to cover the whole wrist range of motion. To minimize joint misalignment and avoid unwanted relative movements between the wrist and the robot during the experiment, their arm was firmly secured to the rigid cast by Velcro[®] strips. Subjects wore opaque glasses and noise-canceling headphones to avoid visual and acoustic interference and were instructed to maintain a relaxed hand grip to avoid fatigue (Figure 2.3A).

Participants underwent a unidirectional 2-alternative-forced-choice (2AFC) discrimination paradigm in which the Standard stimulus S and the Comparison stimulus, shown in Figure 2.3B were presented in random order and separated by a 2-second inter-stimulus interval. Participants were requested to discriminate the Comparison by verbally indicating which stimulus moved their wrist to the furthest position from the initial resting one, which was kept constant during the whole duration of the experiment.

The 2AFC discrimination paradigm was used in conjunction with the QUEST algorithm. It is a parametric, adaptive Bayesian method developed by Watson and Pelli [106] which calculates the difference between stimuli of the subsequent trial, also called *Intensity*, based on the last response, converging to the perceptive threshold almost monotonically. The initial comparison stimulus was set to 23° in order to be easily detectable by all the subjects. Subsequent stimuli were obtained by the sum of the QUEST algorithm result and a random Gaussian noise between 0 and a maximum of $\pm 20\%$ of the stimulus. An example of Intensity trend is shown in Figure 2.3C.

Each trial was initiated by the experimenter by pressing a button, after which the two movements were presented at a constant velocity of $6^\circ/\text{s}$ so that the two final positions were presented temporally close enough to enhance the working memory processing the comparison.

Subjects were required to sense wrist angular displacements in the three different DoFs separately (FE, AA and PS) resulting in six different experimental conditions: Adduction, Abduction, Flexion, Extension, Pronation, and Supination. Each session lasted for ~ 45 minutes with a three-minute rest period every 15 - 25 trials required to prevent mental fatigue and enhance attention, which are essential to ensure the validity of the results [107].

The subset of 5 participants performed the same experimental procedure in the flexion condition, resulting in a total of three different test sessions performed on three different days.

2.3.2 Data analysis and results

Proprioceptive acuity was evaluated as JND between Standard and Comparison stimuli for the six wrist configuration. The percentage of responses in which the

Figure 2.4: *Psychometric functions of a single participant for flexion (A) and abduction (B). Circles represent binned responses recorded during the experimental procedure; vertical line depicts the mean (acuity threshold) of the Cumulative Gaussian. Data were discretized with a bin size of 0.01° ; thus, every point can correspond to a variable amount of responses. The plot presents threshold of 0.39 and 0.29 in logarithmic scale corresponding to 2.46° and 1.94° in linear scale.*

comparison stimulus was correctly identified as largest displacement was computed across the range of displayed comparison stimuli.

The percentage data were fitted using a cumulative Gaussian function to get the associated psychometric function ψ , which describes the probability that a comparison is correctly recognized as the stimulus with the largest intensity. The psychometric function for the 2AFC test ranges from 50% to 100%, where the lower bound reflects the fact that when the stimuli cannot be identified, the subject guess has 50% probability of being correct, while when the difference between the two stimuli is sufficiently high, the comparison is always correctly identified in absence of lapsing errors. We inspected the data to verify the absence of these errors in the upper asymptote, which affect the shape of the curve and introduce bias in the acuity estimate [108]. Based on ψ , the proprioceptive acuity, or JND, was defined as the difference between stimuli necessary to correctly discriminate the stimuli with a frequency of 75% [109].

Figure 2.4 shows typical psychometric functions obtained for threshold detection in the two DOFs of the wrist joint for one participant. The figure reveals that this subject had a higher discrimination threshold for flexion compared to abduction, but a shallower slope and therefore a more variable judgments for abduction.

Mean values for JND were $2.15^\circ \pm 0.43^\circ$ and $1.65^\circ \pm 0.39^\circ$ for flexion and extension, and $1.52^\circ \pm 0.36^\circ$ and $1.13^\circ \pm 0.34^\circ$ for abduction and adduction, and finally $1.90^\circ \pm 0.58^\circ$ and $1.70^\circ \pm 0.30^\circ$ for pronation and supination. The JND of

the majority of participants was higher for FE than for PS and AA, suggesting a lower sensitivity in discriminating movements along this DoF, consistently with the average values shown in Figure 2.5.

We tested if the time elapsed between the stimuli influenced subject performance. We determined the percentage of responses in which subjects recognized the second and more recent stimulus as the comparison. On average the subjects chose the second stimulus the 43.67% and 44.17% of the trials for FE and AA respectively, showing no bias towards the last stimulus presented.

The analysis of JND from the subset of 5 subjects who performed the test in two additional days (T2 and T3) resulted in negligible inter-test variability (Figure 2.6). The coefficients of test-retest reliability were $r = 0.986$ and $r = 0.971$ respectively for the T2-T1 and T3-T2 comparisons. The mean within-subject variability across all three tests was $s = 0.09^\circ$. The results provide evidence that the method is time independent and the result reliable.

2.4 Feasibility of the wrist robot for proprioceptive evaluation

For the first time, the proprioceptive acuity of the healthy dominant wrist has been obtained in terms of Just Noticeable Difference for its three DoFs.

Figure 2.5: *Average JND and standard deviations of the sampled population. Black and gray bars refer to opposite movements along the same DoF.*

Figure 2.6: *Proprioceptive acuity in terms of JND for flexion movements across three different experimental sessions T1, T2, and T3 tested for a subset of five subjects.*

To establish the data validity, due to the lack of data on the JND of the wrist, we evaluated how these are related to the neuroanatomy of the wrist and to data found in the literature about the proprioceptive acuity of the arm and according to the results reported in Section 2.1.2.

Similarly to the results obtained with the JPM protocol, we found an anisotropy in proprioceptive acuity related to the neuroanatomy of the wrist as discussed in Section 2.2, suggesting the validity of the proposed method.

In terms of similarity with proprioceptive acuities of the upper limb joints, Le-phart et al. found repositioning errors in the range of 12 - 31% of the target joint angle in normal shoulder [110], while, for the elbow, Goble reported in his review, errors in the magnitude of 2.5° [94] and Elangovan et al. reported a mean elbow joint discrimination threshold of 1.05° , or 10% of the standard of 10° [105]. This finding coincides very closely with our results at the wrist joint and shows how the acuities found with a robotic device are within the physiological range of upper limb acuity.

We have also analyzed the test-retest reliability of the protocol and verified that the methodology provides reliable and repetitive estimates of proprioceptive acuity as shown by the excellent reliability, and that the robotic device can be used as a quantitative measuring system for proprioceptive assessment. Given the precision of the motors and sensors of the Wrist robot, we believe that the source of variability of the JND obtained in the different sessions is likely a result of the individual

variability of verbal responses to identical stimuli experienced on different test dates.

The sensitivity of the system is determined by the ability of the device to accurately displace the joint in a given position and to precisely sense it by mean of the encoders. Although the obtained proprioceptive thresholds are higher than motor and sensor resolution of the Wrist device, quantization of motion, which can lead to inaccuracy, must be taken into account. While we cannot fully exclude the presence of misalignments of the wrist joint axes with respect to the axes of the robotic device, the low inter-test variability indicates a high repeatability of the results with a negligible effect of the influence of such misalignments.

Furthermore, we cannot exclude that the nature of the 2-alternative-forced-choice discrimination paradigm could have introduced a bias in participants' responses. Participants were properly trained before the test, and the experiment was designed such that the standard and comparison stimuli were pseudorandomly displayed either as first or second stimulus throughout the whole task. To evaluate subjects bias, we tested for the effect of stimulus order presentation on the percentage of correct responses shown in the psychometric function, which showed no differences.

We can, therefore, affirm that the inherent limitations of both robotic technology and experimental paradigm do not jeopardize the application of robotic technology in the proprioceptive assessment by mean of discrimination threshold. The following section reports the results of a test performed to verify the possibility of generalizing the acuities found and rule out the influence of the stimuli choice.

2.5 Weber's Law and generalization of the Just Noticeable Difference for proprioceptive assessment

Human capability to discern sensory stimuli can be described by the Weber's Law, a historically important psychological law that quantifies the perception of change in stimulus magnitude. The law states that the accuracy of perception of a physical property is constant across a wide range of stimuli amplitudes. As a result, the just noticeable difference is a constant proportion of the standard stimulus value.

Just noticeable differences can be therefore defined in terms of the Weber's frac-

tion k , which reflects the ratio between the threshold (ΔS) and the standard stimulus intensity (S) [111]

$$k = \frac{\Delta S}{S} \quad (2.3)$$

The definition of the Weber’s fraction allows a direct comparison of proprioceptive status obtained with different stimuli amplitudes. Additionally, the knowledge of the Weber’s fraction could lead to significantly shorter tests by reducing the magnitude of the stimuli and can be more tolerated by patients. The knowledge of Weber’s fractions for wrist proprioception can also allow a comparison among different sensory modalities.

2.5.1 Participants and experimental design

Eight participants (mean age $\pm$ SD: 25.5 ± 3.0 yrs.) volunteered for the study evaluating the validity of the Weber’s law. All participants were screened to test their laterality index and gave their informed consent prior to testing.

To evaluate the validity for the Weber’s law for joint position sense, the experimental sessions were divided into four blocks which tested a different amplitude of the S stimulus: 10° , 20° , 30° and 40° . The four blocks corresponding to the different test amplitudes were presented in a randomized fashion across subjects to counterbalance order effect.

In each block, participants underwent a 2AFC discrimination paradigm in which the comparison C and standard S stimuli were randomly presented and separated by a one-second interval in each trial, and movement velocity was set to $15^\circ/\text{s}$. Subjects took a 2-minute rest break after the completion of about one-half of the trials in each block and a 5-minute rest between blocks. The experiment approximately lasted one hour.

For this test, the adaptive procedure used for stimulus selection was an adaptive staircase algorithm [112]. The C stimulus was initially set to $S + \log_{10}(0.8)$ and was reduced after each correct answer until the first wrong response, after which the staircase followed the weighted two-down/one-up rule. With this approach, a wrong response resulted in a stimulus increase of Δ^+ (step up), while two consecutive correct answers resulted in a reduction of the intensity of Δ^- (step down). Δ^+ was set to $\log_{10}(\frac{2}{3}\sigma)$, where σ is the extent over which the psychometric function goes

Figure 2.7: *Staircase for the two-down/one-up rule. The difference between standard and comparison stimulus (log units) changed according to the responses given by the subject. Black circles indicate responses while gray circles indicate the reversal points. After the first reversal, two consecutive correct responses resulted in a smaller difference between stimuli. One incorrect response resulted in a larger difference.*

from the lower to the upper asymptote. According to the psychometric functions found with the method described in the previous sections, σ was set to 2.5° . Prior to the first error, Δ^- was set to 0.8 and the intensity was reduced after a single correct answer to reducing the number of trials necessary to converge to the discrimination threshold. Subsequently to the first reversal, Δ^- changed to 0.17.

Each participant performed a number of trials which resulted in 16 reversals of the staircase representing changes in the C stimulus.

As the threshold has been defined as the 75% of probability of correctly recognize the C stimuli, the step down and step up sizes were chosen according to the following criteria. Let Ψ be a monotonic increasing psychometric function and x the stimuli difference, $\Psi(x)$ the probability of correct answer and $1 - \Psi(x)$ the probability of giving the wrong answer. As explained by Kaernbach [113], the equilibrium condition for any convergence point in $\Psi(x)$ is

$$\Delta^- \Psi(x_0) = \Delta^+ (1 - \Psi(x_0)) \quad (2.4)$$

When using a transformed up/down method in which the number of correct answers that decreases the intensity is higher than one, the equation becomes

$$\Delta^- f(\Psi(x_0)) = \Delta^+ (1 - f(\Psi(x_0))) \quad (2.5)$$

where f is the transformation for the up/down method chosen [114]. Rearranging the formula it is found that

$$\Psi(x_0) = f^{-1} \left(\frac{\Delta^+}{\Delta^- + \Delta^+} \right) \quad (2.6)$$

When setting $\Psi(x_0) = 0.75$ and choosing the two-down/one-up rule it results that

$$\Delta^- = 0.778\Delta^+ \quad (2.7)$$

2.5.2 Data analysis and results

In order to verify that the Weber's law holds for proprioception, the JND was computed for the four experimental conditions separately. For each participant, the staircase was analyzed and the first two reversals were excluded. The JND was computed as the average of the remaining 14 reversals in logarithmic scale [114, 115]. The resulting JNDs were finally converted in linear scale and both the linear and logarithmic results for all subjects were checked for normality with a Shapiro-Wilk test. Previous studies have indeed shown that JNDs follow a normal distribution only in the logarithmic scale [116]. Means of the normal data were then considered to determine the Weber's fractions for the four different S stimuli, which were then analyzed with a one-way repeated measures ANOVA to assess the effect of stimulus magnitude. A preliminary analysis of the test assumption of sphericity was performed with the Mauchly test. Differences were considered significant if the p-value was < 0.05 . The linear regression was then performed on mean thresholds for the four different S stimuli, and a single value for the Weber fraction was defined as the slope of the fitting line.

The Shapiro-Wilk test confirmed that thresholds in linear scale followed a normal distribution (all p 's > 0.05). Means and standard deviations were therefore calculated in the linear domain. JND obtained ranged from 1.45° (SEM = 0.21) for S stimulus equal to 10° to 4.34° for S stimulus equal to 40° (SEM = 0.81). S stimulus of 20° resulted in a JND of 2.07° (SEM = 0.57) while a JND of 1.93° (SEM = 0.38) was found for S stimulus of 30° . The corresponding Weber's fractions were respectively 0.15, 0.10, 0.06 and 0.11. The Mauchly test reported no violations of the test assumptions and the statistical analysis resulted in a non-significant effect

Figure 2.8: *Discrimination thresholds + SEM for the four standard stimuli tested and regression line used to determine a single value for the Weber’s fraction, equal to the slope of the line.*

of the S stimulus magnitude $F_{(3,5)} = 4.479$, $p = 0.07$.

A linear regression procedure was employed to fit the mean data resulting in $\Delta S = 0.09S + 0.31$ from which the Weber’s fraction of 0.09 was obtained. The coefficient of determination was computed to be $R^2 = 0.73$, suggesting a good correlation between the discrimination thresholds and the S stimuli.

2.6 Weber’s fractions for wrist proprioception

The assessment of proprioception and its sub-modalities provides a valuable set of information for determining the efficacy of treatment in patients with sensory impairments. The evaluation of the Weber’s fraction for joint position sense and the other sub-modalities can help to determine which sensory pathways have been compromised by brain injuries.

In this study, we determined whether the Weber’s Law holds for proprioception, with the goal of providing a metric for proprioceptive acuity which is independent of the choice of the standard stimulus employed in the psychometric test. The analysis of the data collected from eight subjects reports that the JND follows the behavior predicted by the Weber’s Law resulting in a Weber’s fraction of 0.09. This result is in line with the fraction previously found for displacement of the forearm [117] and with the elbow proprioceptive acuity obtained using the psychophysical method of this study [105]. Moreover, the JND for wrist passive movements is similar to the one obtained for the discrimination of forces at wrist level obtained from a

psychophysical method (Weber's fraction = 0.11) [118].

When evaluating the Weber's fraction for wrist flexion, the resulting value of 0.14 for a movement extent of 15° at the velocity of $6^\circ/\text{s}$ is similar to the Weber's fraction obtained for movements of 10° , suggesting a limited effect of velocity on proprioceptive acuity for passive movements and the reliability of the result.

2.7 Summary

In this chapter, we reported the proprioceptive acuity of the wrist joint of healthy participants evaluated by mean of a robotic interface and the generalization of such result. Our findings provide evidence for the feasibility of robotic-aided proprioceptive assessment: robotic technology can generate robust, repetitive, reliable and unbiased metrics for the assessment of joint position sense. If implemented in clinics, it would avoid the problem of the poor inter-rater reliability and the high variability often found in the clinical scales. Moreover, as the wrist robot can deliver rehabilitation intervention as well as proprioceptive assessment, it could potentially reduce the costs associated to the amount of individual attention from clinicians and therapists and the cost associated to the diagnostic, which is implemented with additional software and minimal hardware enhancements.

The evaluation of the Weber's fraction expands the potentiality of the assessment, which could transcend the particular hardware and stimuli chosen and provide a standard method to collect standardized data easily comparable with those collected worldwide.

Chapter 3

Factors affecting wrist proprioception: handedness, target presentation modality, and external forces

Proprioception provides information about limb configuration which is essential for planning and controlling the motor output. While it has been demonstrated that the motor behavior is affected by limb dominance, it is still a matter of debate whether handedness, the preferential use of one hand for fine motor activities, affects proprioceptive perception and if the motor dominance is reflected in the sensory system. Similarly, as most of sensory experiences are gained by active exploration of the world, sensory events resulting from our own action may be coded differently from changes in the environment. It is also a matter of debate how different external dynamics which result in various motor commands affect proprioception.

To answer these questions, in this chapter we report the outcomes of three studies. In the first one, proprioceptive acuity of the non-dominant wrist is evaluated and compared with the dominant side. We then evaluated the effect of the presence of motor command and afferent signals on proprioceptive performance as well as the robustness of wrist position matching accuracy under external forces.

The results presented in this chapter can be found in [119–122].

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3.1 Laterality in the sensory system

The asymmetries in limb preference when performing daily living is a distinct mark of lateralized brain function [123]. The tendency to use a preferred hand for motor activities is commonly referred as handedness, and commonly favors the use of the right arm: approximately nine out of ten individuals prefer to use the right arm to perform selected tasks [124].

Motor behavior studies have shown that dominant and non-dominant arms have separate functional roles: while the preferred arm is specialized in the control of trajectory, the non-preferred arm is specialized in setting the reference positions or postures for the activity of the dominant one [125]. As a consequence, there is evidence that the preferred arm relies on visual feedback whereas the non-preferred arm is enhanced for proprioceptive feedback processing [126].

The majority of the studies on proprioception have focused on the dominant limb of right-handed individuals [127–129], and the effect of hand dominance on proprioception is still under debate. In fact, the limited amount of studies on the asymmetry in proprioceptive functions have produced contradicting results which can be attributed to differences in the protocol employed. Matching methods can incorporate different delays, can be performed with or without vision and can involve

planar or spatial movements. In addition, the matching can involve a sequential movement of one or both limbs or a simultaneous movement of both limbs.

For example, results obtained with these matching methods have been shown to differ when the matching involves a previous position reached by the same limb or when the contralateral limb has to reproduce the other limb position [130].

Furthermore, proprioceptive asymmetries at the level of the wrist have received less attention. The importance of quantification of proprioception of the distal components is relevant especially in clinical issues, where collateral effects of brain damages are often associated with proprioceptive loss.

We have therefore test proprioception by mean of two different protocols to determine the effect of handedness on its acuity:

- Psychophysical threshold or just noticeable difference (JND);
- Joint position matching method (JPM).

In the joint position matching method, discussed in Section 2.1.1, the user is asked to voluntarily move his limb to a pre-defined target position and the acuity is measured as the positional error between the target position and the final point reached with the Matching movement. As introduced in Section 2.3.1, the psychophysical threshold represents the Just Noticeable Difference (JND) between the amplitude of two movements that can be recognized the 75% of the time.

By employing the same robotic system, the following sections report the characterization of the proprioceptive acuity of the left wrist of healthy right-handed subjects in the flexion/extension (FE) and abduction/adduction (AA) DoFs. Subsequently, the difference between acuity in abduction and flexion of the dominant and non-dominant wrist are discussed in relation to the results presented in Chapter 2.

3.1.1 Participants and assessment protocol

Fourteen participants (mean age 26.9 ± 3.86 years, 6 females, 8 males) participated in the study evaluating errors during an active matching. Six healthy subjects, (mean age $\pm$ SD = 26.7 ± 2.16 years) participated in the experiment evaluating the acuity as JND. After providing the informed consent to the study, all subjects sat beside the robot with their left arm restrained on the cast by Velcro[®] strips, and

they wore opaque glasses and noise-canceling headphones in order to avoid visual and acoustic interference. In order to test the participant’s matching performance of the non-dominant wrist, they underwent the JPM test as described in Section 2.1.1) which is summarized as follow. Auditory cues marked the start of the passive reaching phase, in which the wrist was passively moved by the robotic device to specific target positions (FE: 32° , AA: 16°) and held there for three seconds. The wrist was passively returned to the initial start position after which another sound notified the beginning of the active replication of the target angle without interaction forces from the robot. The Matching movement was considered completed and the perceive target position reached when the movement speed was lower than a velocity threshold of $2^\circ/\text{s}$ for more than two seconds.

Participants performed 12 Matching movements for each DoF evaluated (24 trials in total). Trials across DoFs were presented in a pseudo-random fashion and the entire experiment lasted approximately 30 minutes.

In order to test the JND of the participants, the experiment was split into two sessions which employed the same methodology of the procedure described in Section 2.3.1. Briefly, a unidirectional 2-alternative-forced-choice (2AFC) discrimination paradigm was used for the four conditions (Abduction, Adduction, Flexion, and Extension). Each trial consisted in the presentation of two angular displacements in one direction among which subjects were asked to indicate which had the greatest amplitude. The standard stimulus S, was constant during the experiment and set to 15° , while the magnitude of the comparison stimulus C, initially set to 18° was updated by the QUEST algorithm [106]. Also in this experiment, stimuli were presented in a random order and separated by 2 seconds, and the reaching velocity was set to $6^\circ/\text{s}$. The same procedure was applied to the dominant wrist of five of the six subjects. They were presented with two conditions: Flexion and Abduction. Each experimental session consisted in 50 trials for condition, leading to a total of 200 trials for the first session and 100 trials for the second, both with an interval of five minutes of rest between conditions.

3.1.2 Data analysis and results

The joint position matching performance was evaluated by mean of the metrics presented in Chapter 2: Absolute Error and Variability. We included an analysis

of Matching movement kinematics, measured through the *speed* and the movement *smoothness* [82]. *Speed* is the mean of the average velocity $\dot{\theta}_i$ of each Matching movement across N trials:

$$Speed = \frac{\sum_{i=1}^N \dot{\theta}_i}{N} \quad (3.1)$$

Movement *smoothness* depends on the average across N trials of the number of peaks (*npeaks*) in the Matching movement speed profiles, and is computed as:

$$Smoothness = \frac{\sum_{i=1}^N 1/npeaks_i}{N} \quad (3.2)$$

Differences in proprioceptive acuity and kinematics were subjected to a Repeated Measures ANOVA with Hand and Direction as factors. Results with p values < 0.05 were considered significant. Post-hoc analysis of significant main effects and interactions was performed with Bonferroni-corrected paired t-tests.

The JND was evaluated as the final difference value between comparison and standard stimulus obtained by the QUEST algorithm. To assess the presence of asymmetry between non-dominant and dominant wrist acuity, we performed an un-balanced one-way ANOVA to compare the obtained thresholds for the non-dominant hand with the ones obtained for flexion and extension of the dominant hand presented in the previous chapter.

Laterality on JPM

Mean absolute error $\pm$ SD for the non-dominant wrist across all movements was $3.65 \pm 1.90^\circ$ which was similar to the dominant hand ($3.61 \pm 1.83^\circ$) as confirmed by the statistical analysis, $F_{(1,13)} = 0.02$, $p = 0.88$. An effect of movement direction was found, $F_{(3,39)} = 2.90$, $p = 0.047$, and the post-hoc analysis revealed a significant difference between movements in the FE DoF (mean difference = 1.30°), $p = 0.03$.

Similarly, Variability was not affected by Hand, $F_{(1,13)} = 0.02$, $p = 0.91$, and mean values across subjects and directions were $2.87 \pm 1.39^\circ$ and $2.90 \pm 1.14^\circ$ for the non-dominant and dominant hand respectively. Again, an effect of Movement was found, $F_{(3,39)} = 20.83$, $p < 0.001$, with higher Variability in the FE DoF ($3.20 \pm 1.44^\circ$) compared to AA ($2.26 \pm 0.69^\circ$). Multiple comparisons revealed significant differences in Variability between Flexion and both directions in the AA DoF as well as Extension and AA (all adjusted p 's < 0.003).

Figure 3.1: *Wrist proprioceptive metrics and kinematics (mean $\pm$ SD) for the dominant and non-dominant sides.*

Kinematic metrics gave different results: while Speed was not significantly affected by Hand ($F_{(1,13)} = 1.23$, $p = 0.29$), an effect of Hand was detected for Smoothness ($F_{(1,13)} = 8.15$, $p = 0.01$). Mean Speed was $69.2 \pm 22.4^\circ/\text{s}$ for the non-dominant hand and $72.5 \pm 31.3^\circ/\text{s}$ for the dominant one. Smoothness value was higher for the non-dominant hand (0.60 ± 0.32) compared to the dominant (0.35 ± 0.229). An effect of Movement was found only for the Speed metric, $F_{(3,39)} = 87.58$, $p < 0.001$. Movements were significantly faster in the FE DoF ($90.9 \pm 21.0^\circ/\text{s}$) compared to the AA DoF ($50.8 \pm 15.1^\circ/\text{s}$). Post-hoc analysis showed significant differences in Speed between Flexion and both directions in the AA DoF as well as Extension and AA (all adjusted p 's < 0.001).

Laterality on JND

The smallest JNDs were obtained for the AA DoF: mean acuity $\pm$ SD = $1.26 \pm 0.29^\circ$ and $1.31 \pm 0.32^\circ$ for adduction and abduction respectively. Higher mean acuities were obtained for FE: $1.33 \pm 0.38^\circ$ and $1.63 \pm 0.42^\circ$ for extension and flexion. These results are shown in Fig 3.2. Thresholds resulted smaller for extension in FE movements and, when the movements were performed in AA, acuity for adduction was greater than abduction in five out of six subjects.

Compared to the results obtained for the dominant wrist during abduction and

flexion movements, subjects showed higher acuity for movements performed with the non-dominant wrist, as depicted in Table 3.1. From data recorded during the second part of the experiment we obtained higher thresholds: mean $\pm$ SD = $1.64 \pm 0.40^\circ$ for abduction and $2.14 \pm 0.60^\circ$ for flexion, although the main effect did not reach the 0.05 level of significance ($F_{(1,14)} = 4.58$, $p = 0.05$ for the flexion condition and $F_{(1,14)} = 1.05$, $p = 0.32$ for abduction).

Figure 3.2: *Bidimensional representation of the non-dominant wrist proprioceptive acuity. The x-coordinate represents flexion/extension (FE), while the y-coordinate refers to adduction/abduction (AA). Empty circles represent the thresholds for each subject, filled circles are the mean threshold for each movement. Acuity is greater for extension for movements in FE and adduction for AA.*

Table 3.1: *Results for the test performed by 5 participants with the non-dominant (ND) and the dominant (D) wrist.*

	Abduction ND	Abduction D	Flexion ND	Flexion D
<i>S1</i>	1.58°	1.76°	1.41°	1.94°
<i>S3</i>	0.85°	1.16°	1.68°	2.75°
<i>S4</i>	1.50°	1.38°	1.35°	1.88°
<i>S5</i>	1.07°	1.68°	1.32°	1.38°
<i>S6</i>	1.19°	2.21°	1.58°	2.73°

3.2 Wrist proprioceptive acuity and handedness

Proprioception of the non-dominant wrist has been evaluated with two different paradigms by mean of a robotic device, which provides an accurate and less variable estimate of its acuity. We found that, similarly to the results obtained for the dominant wrist (see Chapter 2), non-dominant wrist proprioception is not homogeneous across its DoFs and that the acuity can be correlated to the ratio between final position and the portion of the ROM tested. Considering that the initial position of the wrist was set to 0° (JPM task) and 10° (psychometric task) in adduction, movements in AA (16° and more than 15° for JPM and psychometric tasks respectively) cover a larger portion of the RoM, which is $\sim 35^\circ$ compared to the flexion condition, in which the wrist displacements were 32° (JPM task) and more than 15° (psychometric task), for a RoM of $\sim 75^\circ$ for men between 20 and 29 years old [131].

Regardless of test employed, we found no evidence of asymmetries in proprioceptive performance: JND, matching errors and variable errors recorded for the two wrists were indeed similar, in line with the studies of the groups of Carson, Chapman and Bullock-Saxton [132–134]. This result contradicts the findings of Goble et al. [94, 126, 135] that the non-dominant limb has superior proprioceptive sensitivity than the dominant limb and suggesting a specialization of the right hemisphere/left arm for proprioceptive feedback processing. The difference in results can be attributed to a site-specific asymmetry, as these studies have measured proprioceptive performance during matching of elbow target positions. A study of Roy and MacKenzie found that healthy individuals display a higher accuracy when matching the non-dominant thumb position while no differences were detected during dominant and non-dominant arm position matching [136]. Differences in results can also be related to the differences in methodology employed to assess joint position sense. In a study by Adamo and Martin, differences between ipsilateral and contralateral matching performance of the wrist were evaluated [130]. The authors found that absolute errors were similar independently from the hand tested in the ipsilateral test, during which the same wrist performed both the criterion and matching movement. Matching errors were found to be greater during the contralateral test, in which participant matched the target configuration, displayed with one wrist, with the opposite one. Further, the direction of these errors was different when matching with the right or left wrist, suggesting that asymmetries exist in the central processing

of proprioceptive information.

The results here obtained seem to suggest that proprioceptive processing is independent from the hemisphere specialization observed for movement and position control proposed by Sainburg [125]. However, we believe that the absence of asymmetry is due to differences between proprioceptive gains for the right and left wrist, according to the proprioceptive sensory-motor gain hypothesis [130]. As the matching involved ipsilateral movements of one wrist, the perception of the target position is not affected by the perception provided by the opposite wrist, which is expected to be different when considering the anatomical differences between the dominant and non-dominant sensorimotor systems. This hypothesis is tested in the next chapter, in which the contralateral test is employed to determine if the use of both wrists reduces the matching accuracy and precision due to the difference in perception of the dominant and non-dominant hemispheres.

3.3 Matching performance during active and passive target replication

So far, we have evaluated proprioception of the dominant and non dominant wrist in presence of passive movements (psychophysical method of JND) and during the active matching of a passively reached position (joint position matching). In this last test, the subject's joint is moved by the experimenter or, in our case by the robot to the target position during the so-called Criterion movement and returned to the initial position, after which the active Matching movement starts. Therefore, while the psychophysical method compares two passive movements, the joint position matching method compares a passive and an active movement. During activities of daily life, the majority of our sensory experiences are gained by active exploration of the world and it is not clear whether sensory events resulting from our own action (reafference), such as the Matching movement, may be coded differently from changes in the environment (exafference), such as the criterion movement [137].

As introduced in Chapter 1, the primary receptors for proprioception, the muscle spindles, are able to signal the joint position as well as both passively experienced movements and movements that are produced volitionally. Differently from the joint receptors, which fire in comparable manner during active and passive movements,

muscle spindles signals are greatly increased even with small active displacements due to the sensitivity to change of length of the muscle [102]. During a passive movement, which does not involve muscle contraction, joint position sense must derive from afferent signals of these receptors whilst during active movements, which are produced volitionally, the motor command signals which are centrally generated have been shown to provide information for kinesthesia. Further, studies from the groups of Gandevia [138] and Smith [139] have shown that in situations where both motor command and afferent signals are available, motor command contributes to joint position sense.

We, therefore, test the hypothesis that matching accuracy would be different for actively or passively presented targets. In this context, a literature analysis revealed that contrasting results have been reported so far. In his study, Kelso [140] compared the matching accuracy of actively or passively presented targets which were chosen by either the experimenter or the subject. The study revealed that matching accuracy is significantly higher when both the Criterion as well as the Matching movement are actively performed only when subjects were left free to choose the target position. On the contrary, there were no differences in performance when the matching involved experimenter-defined positions, regardless of whether subjects actively or passively matched them. A more recent study by Goble and Brown [141] assessed the matching accuracy after an active and passive presentation of elbow target positions and did not find any significant difference between the conditions. Similarly, the results of the study by Shibata and Santello [142] suggest that the presence of voluntary commands during digit matching does not increase the accuracy of estimation of finger position. Adamovich and colleagues [127], instead, provided evidence to support the hypothesis that efference-copy-based predictions of body position improve accuracy when matching a target displayed using active movements. Laufer et al. [143], compared matching errors with a similar protocol involving arm movements as well as movements of a laser pointer after the active and passive displacement to the target position. Interestingly, the results confirmed that errors were lower after an active criterion movement for both movement and visual matching.

In the study reported in this section, we tested how the presence of reafferent signals available during the Criterion movement affect wrist position sense. The

test involved a joint position matching in two conditions which differ in the criterion phase: in the passive condition, the Wrist robot was used to bring the wrist in the target configuration; in the active condition, the target position was visually displayed on the screen and the participant actively rotated the wrist while holding the handle of the robot. To test our hypothesis that the presence of the motor command in both movements would improve proprioception, we measured the precision of the spatial localization as the systematic errors and their variability as well as kinematic indicators such as speed and smoothness of the Matching movement.

3.3.1 Participants and procedure

Ten healthy participants (mean age $\pm$ SD = 27.7 ± 3.2 years, eight males) with no history of sensorimotor disorders volunteered for the study. All participants were screened with the Edinburgh Handedness Inventory and resulted right-handed.

They underwent the joint position matching task (JPM) with the dominant wrist. Also for this test, the participants' forearm was strapped to avoid any shift in position, and the initial position was set to 0° in FE and 10° in adduction. Participants were provided with a visual feedback regarding the angular displacement of the wrist on a screen placed approximately 50 cm away from them (Figure 3.3A). Wrist rotations resulted in a linear displacement of a small sphere while a static larger sphere represented the target position.

During the criterion movement, prompted by an acute sound, the participant's wrist was rotated to match the target configuration in presence of the visual feedback. After three seconds, a return movement brought the wrist back to the initial position for the beginning of the Matching movement, which was prompted by a deep auditory cue. Participants then actively moved their wrist to reproduce as accurately as possible the target configuration in absence of any visual feedback.

The experiment consisted in two blocks in which two conditions, represented in Figure 3.3 were separately performed: *passive-active JPM* (paJPM) and *active-active JPM* (aaJPM). The paJPM condition corresponds to the protocol employed in the studies previously reported, in which the Criterion movement was passively imposed by the robot. In the aaJPM condition, subjects were asked to actively bring their wrist in the target configuration with the help of the visual feedback so that the cursor representing wrist rotation reached the target avatar on the screen.

Figure 3.3: (A) Participant grasping the handle of the wrist robot while watching the visual feedback about wrist angular position on the screen. The vision of the wrist was blocked by a plate. (B) Experimental conditions: for the passive-active joint position matching (paJPM), during the Criterion Movement the wrist is passively moved by the robotic device from the neutral configuration to the target and then positioned in the neutral configuration; for the active-active joint position matching (aaJPM), during the Criterion Movement the wrist is actively moved by the participant from the neutral configuration to the target, after which the robot positioned the wrist in the neutral configuration. Regardless of condition, during the Matching Movement, the participant actively tried to match the target position. At the end of the Matching Movement, the robot positioned the wrist in the neutral condition for a new trial.

After the Criterion and the Matching movement, the robot moved the wrist back to the neutral position in both conditions.

The target presented was set to 32° in flexion, which was matched 10 times per condition. The Criterion movement in the paJPM had a minimum-jerk profile and a peak velocity of $30^\circ/\text{s}$. Participants were split into two group which performed the two conditions in a different order to counterbalance its effect, and the total duration of the experiment was ~ 15 minutes.

3.3.2 Data analysis and results

We evaluated proprioception in terms of *Absolute Error*, *Signed Error* and *Variability*. The *Absolute Error* reflects the matching accuracy, described as the mean error computed across $N=10$ trials between target position θ_T and matched position θ_i as described in Equation 2.1. The *Signed Error* reflects the directional bias of the error as:

$$\text{Signed Error} = \frac{\sum_{i=1}^N (\theta_T - \theta_i)}{N} \quad (3.3)$$

A negative signed error indicates target overshooting, while a positive value indicates undershooting. Finally, the *Variability* is defined as the standard deviation

of the matching position (Equation 2.2)

Wrist kinematics were also analyzed: recorded joint rotations were filtered with a 6th order Savitzky-Golay filter (11 Hz cut-off frequency) and the average *Speed* and *Smoothness* were obtained as described in Equation 3.1 and 3.2 for each active movement. A mixed-design ANOVA tested the differences in matching errors and variability in the two conditions. Order (i.e. aaJPM first and paJPM first) was considered as the between-subjects factor and Condition (paJPM and aaJPM) as the within-subjects factor.

Similarly, we evaluated differences between kinematics recorded in the Matching movement in the paJPM and aaJPM conditions (within-subject factor) and to compare speed and smoothness in the Criterion and Matching movements (within-subject factor) in the aaJPM. Statistical significance was set at $p < 0.05$.

Matching in the paJPM condition was more precise (average errors $\pm$ SD = $3.0^\circ \pm 0.8^\circ$) compared to the aaJPM condition ($3.8^\circ \pm 0.8^\circ$) (Figure 3.4A), as confirmed by the statistical test. While there was an effect of Condition $F_{(1,8)} = 9.84$, $p = 0.01$, the analysis did not detect the effect of Order, $F_{(1,8)} = 2.05$, $p = 0.19$.

Mean signed errors were $-0.8^\circ \pm 2.0^\circ$ and $-1.3^\circ \pm 2.7^\circ$ for the paJPM and aaJPM conditions respectively, revealing the tendency to overshoot the target position (Figure 3.4B). This tendency was found to be independent of Condition ($F_{(1,8)} = 0.312$, $p = 0.592$) and order presentation ($F_{(1,8)} = 3.769$, $p = 0.09$).

Final positions of the Matching movement were less variable for the paJPM condition ($3.1^\circ \pm 0.9^\circ$) compared to the aaJPM condition ($3.8^\circ \pm 0.8^\circ$), $F_{(1,8)} = 5.76$, $p = 0.04$. No effect of Order was detected $F_{(1,8)} = 0.42$, $p = 0.54$. Variability values for the two conditions are reported in Figure 3.4C.

Following the kinematic analysis, we found that the average speed of the Matching movements was similar for the two groups (factor Order), $F_{(1,8)} = 2.20$, $p = 0.17$. Average speed was $17.2^\circ/\text{s} \pm 4.5^\circ/\text{s}$ and $17.5^\circ/\text{s} \pm 6.5^\circ/\text{s}$ for the paJPM and aaJPM conditions respectively (Figure 3.5A), and the ANOVA revealed that these values were not significantly different, $F_{(1,8)} = 0.06$, $p = 0.81$.

An effect of Condition was instead found for smoothness, which was 0.18 ± 0.03 for the paJPM condition and 0.21 ± 0.06 for the aaJPM condition, $F_{(1,8)} = 5.95$, $p = 0.04$ (Fig. 3.5B). Smoothness was not significantly affected by the order of condition presentation, $F_{(1,8)} = 0.45$, $p = 0.52$.

Figure 3.4: (A) Absolute Errors and (B) Signed Errors with the respective standard errors obtained by each subject (left) and box plot for each condition (right). Gray squares represent errors in the passive-active (paJPM) condition, while black triangles are errors in the active-active (aaJPM) condition; (C) Box plot for Variability values recorded for each subject (empty circles); mean value across subjects is represented by a filled circle and the median value is represented by a line.

Figure 3.5: Box plot of (A) Speed and (B) Smoothness in the Criterion and Matching movements during the active-active (aaJPM) conditions and during the Matching movement performed in the passive-active (paJPM) condition; data recorded for each subject is represented by an empty circle, mean value across subjects is represented by a filled circle, the line represents the median value.

The comparison of kinematic measures of the two active movements in the aaJPM condition showed that mean speed in the Criterion movement was 19.0 ± 4.5

°/s (Fig. 3.5A) which was not significantly different from the Matching movement $F_{(1,8)} = 1.18$, $p = 0.31$, regardless of group, $F_{(1,8)} = 2.74$, $p = 0.14$. There was a significant effect of movement for smoothness values: the Matching movement resulted in a greater value compared to the Criterion movement (0.21 ± 0.06 and 0.14 ± 0.03 respectively), $F_{(1,8)} = 18.07$, $p = 0.003$, as shown in Fig. 3.5B. No effect of Order was detected, $F_{(1,8)} = 0.57$, $p = 0.47$.

3.4 Differences between matching of targets actively and passively presented

The experiment presented evaluated the effect of motor commands during the Criterion movement on the accuracy of the Matching movement in terms of error, variability and kinematics of the recognized target position.

In the condition in which the wrist passively reached the target position (passive-active condition, paJPM), absolute errors were significantly smaller compared to the matching movements after an active target display (active-active condition, aaJPM). Moreover, there were no differences between conditions in terms of systematic directional biases, with a general tendency to overshoot the target position. From the analysis of variability, we found that Matching movements stopped in a final position that was less variable in the paJPM compared to the aaJPM condition. Finally, movements were smoother during the matching phase of the aaJPM condition.

These are interesting results if we consider that the available literature suggests that the proprioceptive system is better-tuned to active movements than to passively experienced movements [144], and if we consider the studies mentioned in the introduction section of this study [127, 140, 141]. However, our work is, to our knowledge, the first one investigating the effect of motor commands on wrist proprioception, and differences might be related to the biomechanics and information obtained from muscle spindles of the wrist musculature. In this regard, a study from Jones and colleagues found that during passive and active reaching tasks with similar kinematics, there was a weaker position sensitivity in active compared to passive movements of the wrist despite a stronger spindle firing recorded for active movements [145].

Another difference that can explain the differences in results is that the protocol

implemented allowed participants to formulate a motor plan prior to the Matching movement execution and that participants performed this movement in presence of both kinesthetic and visual feedback. While access to visual information about joint and target position does not result in differences in spindle afference [146], it could have acted as a confounding factor: participants were not aware of the mapping between wrist rotation and the corresponding virtual movement, rendered as a linear displacement. The motor plan initially determined was therefore continuously corrected during task execution, as suggested by the lower smoothness values in the Criterion movement. These adjustments could have decreased the matching performance, as described by Kelso [140]: if the plan is functionally separated from the execution process, such as in the case of matching a position determined by the experimenter or, in our case, kinesthetically matching a visual position, the proprioceptive performance deteriorates.

The worsening of matching accuracy in the active-active condition can also be caused by a faulty integration of the information from the visual and proprioceptive sensory streams. Indeed, the visual target was defined in coordinates in the external space, whereas the kinesthetic target was defined by the wrist angle. To perform the matching task, the comparison involved a target position stored in the visuo-spatial memory, obtained from the Criterion movement, and the wrist coordinates from proprioceptive feedback, which could have led to a source of errors. For instance, Soechting and Flanders [147], found that errors in pointing are a consequence of errors in the transformation of the visually acquired target into the kinematic representation of the arm movement. In addition, Darling and Miller demonstrated that the pointing accuracy was higher when targets were kinesthetically presented compared to the case in which targets were visually presented [148], and Laufer and Hocherman found that reproduction is adversely affected by the conflicting input from both kinesthetic and visual presentation of the target [149].

Another possibility is that participants could have employed a matching strategy which considered movement kinematics, which was different between Criterion and Matching movement. From the velocity analysis, we found that movements were smoother during the matching of the target actively presented, indicating that participants had a higher confidence in their matching ability in this condition [94], possibly affecting the matching performance [100].

In summary, the literature reports a wide range of results, with studies proposing an advantage of active versus passive movements, and others showing no advantage. The results discussed in this chapter indicate a disadvantage, so that motor commands negatively affect the accuracy of joint position sense. This result can be related to the presence of both visual and kinesthetic information, a finding that highlights the fact that a simple framework (i.e., active movements always facilitates sensorimotor integration) is, in fact, untenable and point to considering other task parameters as well as effectors involved in the task.

3.5 Proprioception under external forces

Proprioception provides information necessary to maintain an updated body image or body schema [150], which is perturbed by different external dynamics in our daily life. An extensive analysis of the effect of loads on human movements has been published so far and motor control studies have provided evidence of how humans respond to external forces only if they have influence on the task completion, according to the "minimum intervention principle" [3] and the "uncontrolled manifold hypothesis" [151–153]. It has been found that when humans perform a reaching task with loose spatial and temporal constraints, they change their kinematics before being pushed by a force that had no bearing on the task completion [154]. The human motor system is also able to adapt its representation of dynamics during learning of a motor task [155]. There is indeed some evidence for independent learning of internal models for kinematic and dynamic control of reaching [156] showing the ability of humans to adapt to unstable and perturbative force conditions [157].

Despite the multitude of studies on the effect of external forces on movements, the correlation between environmental forces and their influence on human position sense is limited, and few contrasting results have been reported. Some studies suggest that external forces, which induce the contraction followed by the relaxation of a muscle without affecting its length, affect the spindle discharge rates which, in turn, affect the perception of limb position [158, 159]. External forces result in a worsening of proprioceptive accuracy as suggested by studies in which participants were asked to match actively or passively a target position after exercising on arm in presence of external forces [160–164]. Other studies, on the contrary, support

the hypothesis that proprioception is robust against external dynamics: when a muscle contracts, the signal generated by the fusimotor fibers in the muscle spindles are subtracted out centrally [165, 166] by means of an efference copy of the motor command [167].

Literature about the correlation between proprioception and external forces for various joints is still very limited [168], and we could not find any study which has tested the effect of different force conditions on JPS of the wrist.

In this section, we present the results of a test designed to fill this gap. We have analyzed proprioceptive acuity of the wrist by mean of a position matching task and evaluate differences in performance in five different loading conditions: passive, high resistive, low resistive, viscous and no load.

3.5.1 Participants and protocol

Fifteen right-handed young males participants (mean age $\pm$ SD: 27.73 $\pm$ 2.91 years) with similar biomechanics characteristics were recruited for the study. They had normal or corrected to normal vision, did not have any known neuromuscular disorders and all resulted right-handed after undertaking the Edinburgh Handedness Inventory.

They were asked to sit beside the robotic device and their position was adjusted to match the requirements previously described. The subject grasped the handle of the robot which only allowed movements along the FE DoF in this test, and vision of the wrist and the robot was occluded by a board, similarly to Figure 3.3A. The test involved an ipsilateral joint position matching task in which targets were presented in five different dynamic conditions: Passive (P), High Resistive (HR), Low Resistive (LR), No Force (NF) and Viscous (V) which differ for presence of visual feedback (Figure 3.6A) and presence of torques provided by the robot (Figure 3.6B).

During the Passive condition, the Criterion movement consisted in a movement imposed by the robot to match the target position. An elastic control torque was implemented to attract the wrist to the target:

$$T_P = K_P(\theta_T - \theta_W) \quad (3.4)$$

Figure 3.6: (A) The Joint Position Matching task: Each trial is broken down into Criterion movement, Return Phase, Matching movement and a final Return Phase. Visual Feedback of wrist position is represented as a sphere which has to reach the target position, represented by a bigger sphere. (B) Depending on the loading condition, the four movements can be performed actively in presence of assistance (Passive condition), perturbation (Resistive and Viscous conditions) or no interaction (No Force condition) from an external torque.

where θ_W is the wrist actual position, θ_T is the target position, and $K_P = 5N/deg$ is the stiffness of the elastic field. No visual feedback of target or wrist position was provided to the subject during this condition. After a three-second dwell time, the wrist was returned by the robot to the initial configuration (Return phase) after which the subject was prompted to perform the Matching movement without any robot assistance or visual feedback.

In the Resistive conditions the robot maintained a constant torque to resist movements towards the target position according to the following formulas:

$$\begin{cases} T_R = -T_{HR}(\theta_T - \theta_0)/|\theta_T - \theta_0| \\ T_R = -T_{LR}(\theta_T - \theta_0)/|\theta_T - \theta_0| \end{cases} \quad (3.5)$$

Here, θ_T represents the target, θ_0 the neutral wrist configuration, $T_{HR} = 0.450$ Nm the intensity of the High Resistance field and $T_{LR} = 0.225$ Nm the intensity of the Low Resistance field. In this condition, the Criterion movement included a visual feedback of the target and wrist positions. The Matching movement was performed actively in presence of the same resistive torque and without visual feedback.

During the Viscous condition, a resistive torque proportional to the movement

speed was applied according to the formula:

$$T_V = -B\dot{\theta}_W \quad (3.6)$$

$\dot{\theta}_W$ represents the wrist speed and B is the coefficient of viscosity. Similarly to the resistive conditions, the Criterion movement was actively performed in presence of both torque and visual feedback. The same viscous field was applied in the Matching movement, during which no visual feedback was provided.

No Force condition (NF). The last condition was the No Force condition, during which the robot was not providing any force during the Criterion and Matching movements. Visual guidance was provided only during the Criterion movement.

3.5.2 Performance measures, data analysis and results

Three indicators of proprioception performance were evaluated in the five loading conditions: Absolute Error, Signed Error and Variability. In order to correlate these indicators to the torques applied at the wrist, we also measured the Loading Torque as the peak value of the torque recorded during the Matching movement.

A preliminary analysis of normality by mean of the Shapiro Wilks test was conducted to test the assumption for the ANOVA. Data, which deviated from the normal distribution, were analyzed by nonparametric analyses. Differences among the force conditions were evaluated by a Friedman's test for repeated measures on group data for Absolute and Signed errors. Main significant differences were analyzed with post hoc analysis (Wilcoxon signed rank test) with a Bonferroni correction for multiple comparisons. Variability was analyzed with a nonparametric Kruskal Wallis test in order to investigate the effect of the force condition. Lastly, a single sample t-test was conducted to investigate statistical significance in target under/overshooting by comparing zero and the Signed error.

From the data recorded, we excluded three subjects which exhibited significantly different errors, especially in the high-load conditions (HR and V). They explained that they misinterpreted the instructions and did not memorize the target position but focused on maximising the level of their muscle co-contraction with the goal of challenging the resistive forces.

Results from the analysis of the remaining 12 subjects are shown in Figure 3.7,

Figure 3.7: (A) Absolute error, (B) Variability, Signed Error (C) and Loading Torques (D) averaged across the 12 subjects in the five loading conditions. (E) The relationship between Signed Error and Loading torque and corresponding regression line.

which reports means and standard errors of the 4 indicators of proprioception and torque in the five loading conditions.

The loading condition affected the Absolute Error as confirmed by the Friedman's test [$\chi^2(N = 72, df = 4) = 13.62, p < 0.01$]. The post-hoc test detected significant differences only between the LR and V conditions ($z = 3.59, p < 0.001$).

A significant effect of force condition was found for the signed error [$\chi^2(N = 72, df = 4) = 75.19, p < 0.001$], and the post-hoc analysis revealed significant differences between the viscous condition (V) and all the other conditions (V-HR: $z = 3.74$; V-NF: $z = 6.41$; V-LR: $z = 5.73$; V-P: $z = 6.01$, all $p < 0.001$). Significant differences were also found between HR and NF conditions and between the HR and P conditions (HR-NF: $z = 5.07$; HR-P: $z = 3.88$, both $p < 0.001$). During the HR and V conditions, which displayed a high loading torque, participants undershoot the target (single sample t-test for HR ($t(71) = -2.590, p = 0.011$) and V ($t(71) = -8.66, p < 0.001$). For the NF condition the bias was opposite: participants tended to overshoot the target, and this bias was significant, ($t(71) = 3.507, p < 0.001$). The LR and P conditions were found to be approximately bias-free.

The analysis of Variability performed by the Kruskal-Wallis test did not detect

significant differences among conditions [$\chi^2 = 0.67, df = 4, p = 0.96$].

The loading torque was 0 Nm for the NF and P conditions; the constant torques in the HR and LR conditions were respectively 0.450 and 0.225 Nm while for the V condition it reached a peak of 0.52 ± 0.04 Nm. A linear regression analysis was used to define the relationship between signed error and loading torque. The least squares fit line (Equation 3.7, shown in Figure 3.7E) resulted in a $R^2 = 0.86$ highlighting a strong linear relationship ($F_{(1,3)} = 19.32, p = 0.02$).

$$MB(LT) = 10.20LT - 1.85 \quad (3.7)$$

3.6 Matching accuracy independence from loading condition

Joint position sense and the sense of force, which originate from the same multi-sensory integration process, should be grossly independent to be functionally effective in the course of skilled control of action. The two submodalities are commonly tested respectively by the Joint Position Matching and the Force Reproduction tasks [117, 161, 169]. These tests reduce the interaction of the other submodality by eliminating interactions with external forces in the case of the matching task or by employing an isometric task such that the force exertion is not accompanied by a joint rotation in the case of the force reproduction protocol. However, activities of daily living are performed in presence of variations of both position and force, and in this study, we tested if the central nervous system is capable to single out the position-dependent and force-dependent aspects of proprioception.

In terms of matching Absolute error, the only significant difference was found between the Viscous and Low-Resistive conditions, which were respectively the conditions with the highest and lowest torques. We also found a higher standard deviation in Absolute errors in the High-Resistive and Viscous conditions which could be due to the fact that torques were not adjusted to the maximum voluntary contraction of each subject. Moreover, these conditions were the ones in which participants underestimated target positions and, interestingly, they also were the conditions in which participants resisted the torques with the largest magnitude.

The stretch imposed to the extensor muscles as a result of the high torque at

the wrist could have increased the spindles discharge rate, which is proportional to the stretch [170], causing the central nervous system to interpret the peripheral information to originate from a longer muscle and therefore a more flexed joint. Another explanation for this finding is that the torque magnitude could have prevented participants to reach the target position.

Despite differences in Absolute error magnitude, we found a similar matching performance among the different force fields in terms of Variability. This result can be surprising when considering findings from different authors who showed that force sensation is negatively affected by fatigue or partially anesthetization of muscles [169, 171, 172]. Our finding, therefore, suggests that different inputs could have contributed to the perception of joint position when perturbed by external forces.

However, information from muscle receptors is integrated with signals of central origin (motor command) to provide proprioceptive information. The central command, or sense of effort, could, therefore, have provided primary information for the recognition of the target position in presence of external forces which are responsible for the reduction of sensitivity for the peripheral receptors.

Moreover, a recent study has provided evidence of a link between motor and sensory areas in the cerebral cortex [173], and the degree of activation of motor areas is directly expressed by the effort sensation. As the muscle is weakened, for instance as a result of fatigue due to a resistive force field, the motor command is increased in order to achieve the desired outcome. This results, in our case, in an increment of effort sensation when moving the handle against the external resistive torques from the robot [117, 174].

3.7 Summary

We evaluated the proprioceptive acuity of the non-dominant wrist of healthy subjects employing a robotic device that provides accurate and reliable results. The results did not differ from acuity obtained for the dominant wrist, suggesting that proprioception is not affected by lateralization. The evaluation of the interaction between reafferent and exafferent signals generated during active movements in the JPM test showed that acuity results higher when participants match the target position after it has been passively displayed. Finally, accuracy and precision in target

matching do not change significantly as a function of an external load, suggesting that the multi-sensory integration process is indeed capable of discriminating different sub-modalities of proprioception (joint position sense and sense of force).

Chapter 4

Sensory integration during bimanual manipulation and bimanual proprioception

To date, there is scant research into the manual lateralization and role assignment in the processing of sensory feedback during coupled bimanual tasks. Moreover, the mechanisms used by the central nervous system to process proprioceptive information during these tasks is still a matter of debate. Contrasting evidence has been provided so far: from one side, some studies report that bilateral proprioceptive performance is lowered to the level of the lower performing limb, while others report that the central nervous system is aware of and utilizes information obtained by the limb with the best proprioceptive acuity for bimanual judgments.

In this chapter, we first present a study which investigated the roles of the dominant and non-dominant hands during a bimanual task in which visual and haptic feedback regarding object penetration were manipulated. The second study examined asymmetries in wrist position sense for proprioceptive tests performed in the unimanual and bimanual mode.

The results presented in this chapter can be found in [120, 175].

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Charmayne ML Hughes, Pietro Morasso and Lorenzo Masia, Robotic assessment of manual asymmetries in unimanual and bimanual wrist joint position sense, Biomedical Robotics and Biomechatronics (BioRob), 2016 6th IEEE International Conference of the IEEE, 2016.

4.1 The role of visual and haptic feedback during dynamically coupled bimanual manipulation

The ability to skillfully manipulate objects is one of the cardinal and distinctive features of human behavior. With practice, an individual is able to gradually learn how to master the most complex skills, such as playing an instrument, high precision assembling, or performing surgical operations.

Since the initial contributions from Shadmehr and Mussa-Ivaldi [155], there has been continuous interest in elucidating the mechanisms underlying the formation of manual skills. Motivated by the fact that many everyday actions involve the use of both hands, a number of bimanual haptic devices and robotic paradigms have been developed to probe the mechanisms of bimanual coordination as extensively reported in [176]. Two basic scenarios have thus far been investigated: *uncoupled independent control*, in which the two hands act separately in manipulating different objects, and *dynamically coupled control*, in which the two hands cooperatively manipulate the same object.

Uncoupled independent control is the most studied of the two scenarios, and primarily utilizes force field adaptation paradigms during symmetric or non-symmetric bimanual actions [177]. During these tasks, participants perform reaching movements with both hands (in non-overlapping workspaces) toward different targets under the effect of force fields. Results of these studies have reported that the process of learning velocity-dependent force fields during a bimanual task is similar for both the dominant and non-dominant hand, regardless of whether a force-field was applied or not (i.e., under a null field) [177].

Nozaki and Scott [178,179] examined the transfer of learning between unimanual and bimanual actions during reaching movements when a velocity-dependent force field was applied to the non-dominant left arm. Those studies demonstrated that there is partial transfer between contexts, indicating that there is a limited overlap of

unimanual and bimanual learning processes beyond the adaptation effects. This finding is supported by neuroanatomical studies indicating that bimanual movements require interhemispheric communication [180], and are associated with greater activation of the bilateral primary sensorimotor cortex (SM1), supplementary motor area (SMA), cingulate motor area, dorsal premotor cortex (PMd), and posterior parietal cortex (PPC) [181].

Bimanual force field adaptation in uncoupled environments was also investigated by Casadio et al. [182] by inducing spatial coupling in two separate workspaces and identifying possible interference effects. In this study, participants reached for the same target while two identical manipulanda applied velocity-dependent non-zero curl viscous force fields to the two hands in either the same (e.g., clockwise for both hands) or opposite orientations (e.g., clockwise for the left hand, counter-clockwise for the right hand). Results indicated that the two arms were able to adapt to the two force fields, but that adaptation was incomplete when the force fields moved in opposite directions. On the basis of these results the authors argued that the neural mechanisms underlying bimanual movements oppose actions that may lead to a crossing of the hands, and postulate that there are two task dependent modules underlying motor-cognitive processing during bimanual actions: an adaptive control module and a “protective” one that opposes potentially “dangerous” bimanual interactions, such as hand crossing.

Dynamically coupled control scenarios have been explored in experiments in which the use of both limbs is synchronously involved to complete a specific task. In Jackson and Miall [183] participants performed dominant right arm reaching movements to a visual target, while a velocity dependent force that was proportional and perpendicular to movement direction acted on their stationary left hand at the same time as the right hand movement. Results revealed that left hand movements peaked just before those of the right hand, indicating that individuals used a predictive forward internal model in which the sensory consequences associated with the right hand were predicted and used to generate an appropriate compensatory response for the left hand.

In a later study, Howard et al [184] used a dual robotic planar manipulandum to examine the transfer between coupled and uncoupled scenarios during a center-out movement in the presence of a velocity dependent force field. Results suggested

that the motor system may use partially separate representations for coupled and uncoupled contexts and that there also exist partially independent representations of the dynamics of the two arms.

Although the aforementioned studies have provided a number of insights into bimanual planning and related control processes underlying motor adaptation, the role of sensory feedback on bimanual coordination has received much less attention. Indeed, the majority of robot-mediated experimental paradigms have provided both visual and haptic feedback to participants. There is evidence that the integration of these sensory streams is weighted based on information reliability and appropriateness [185], and is combined in a complex way which leads to enhanced task accuracy and performance [186]. With respect to bimanual tasks, the coordinated use of the limbs is highly weighted by the dominance of one hemisphere with respect to the other, with the dominant and non-dominant hands adept at utilizing different sensory information. In particular, the literature suggests that the right hemisphere (of right-handers) is more adept at utilizing haptic feedback [187], whereas the left hemisphere (of right handers) is more adept at utilizing visual feedback [188] that ensures accurate interactions between the preferred right hand and the to-be-manipulated objects.

Given the open questions regarding the allocation of functional roles to the hands, and how sensory feedback is used to ensure accurate task performance during dynamically coupled bimanual tasks, the aim of the present work was to examine how visual and haptic feedback is weighted when individuals manipulate an object during a dynamically coupled bimanual task. To this end, participants performed a bimanual grasp and reach task, in which they used two wrist haptic devices to grasp a virtual object and transport it across the workspace towards a target. Four different feedback conditions were simulated: a *Haptic* condition in which participants were provided with haptic rendering of the collision of the wrists' end effectors with the object to be manipulated, a *Haptic+Visual* condition in which participants were provided with both haptic and augmented visual feedback about the end effector penetration inside the object during manipulation, a *Visual* condition in which visual feedback about object penetration (but no haptic feedback was provided), and a *No Feedback* condition where both visual and haptic cues about end effector penetration were absent and participants could rely only on a standard visual feedback

to perform the task.

We were specifically interested in whether bimanual coordination is influenced by the availability of visual and haptic feedback. Based on the literature indicating that the integration of information from different sensory sources augments the precision of the combined estimate [189–192], and that additional visual feedback allows for better control of force when combined with the haptic feedback for unimanual grasping [193], we hypothesized that task performance would be facilitated when participants are provided with both haptic and augmented visual feedback about the object penetration depth (Haptic+Visual condition) compared to when feedback is provided from a single sensory source (Visual and Haptic conditions). In addition, based on the literature suggesting hemispheric specialization during object manipulation tasks [187,188], we expected that interlimb coordination would be influenced by the position of the target [194]. We tested the hypothesis that additional visual information on object penetration would differently affect movements in opposing directions, when the roles of the dominant and non-dominant hands are reversed to superimpose forces and aim at different target locations.

4.1.1 Participants and protocol

Twelve neurologically healthy individuals (mean age $\pm$ SD= 25.6 $\pm$ 2.7, 11 males) participated in the study. All participants were right-handed (mean handedness $\pm$ SD = 90 $\pm$ 7.84), as determined by the Edinburgh Handedness Inventory, and had no history of previous musculoskeletal or neurological disease. Each participant signed a consent form prior to the experiment.

The experiment employed a bimanual workstation consisting of two identical wrist robots. The bimanual task consisted of a grasp and reach movement in which two end effectors (representing the position of the two wrists) interacted with an object which had to be picked and moved towards different targets (Fig 4.1A). In the present study, movements were limited to two DoFs by blocking the PS joints of each of the wrist robot. The virtual environment was simulated using a Simulink model that employed the QUARC Visualization Toolkit. The position of the two end effectors was represented as two spheres that were identical in appearance for both the left and the right wrist. In this way, the participant could use the spherical end effector to grasp the virtual object and to transport it to the target position (Fig.

Figure 4.1: (A) View of the bimanual workstation when operated by the participant. (B) Wrist movements control the position of objects presented in the virtual environment. (C) Schematic of the implemented bimanual controller that provides haptic and visual feedback during object manipulation. (D) Impedance control scheme used to simulate the haptic environment.

4.1B). The position of the end effectors was measured by evaluating the device's joint angles and consequently determining the linear relationship between angle and planar position and multiplying for an opportune scaling factor: flexion/extension and abduction/adduction respectively corresponded to the horizontal and vertical displacement of the end effectors on the screen (Fig. 4.1C). The mapping factor from angles in joint space to linear movement in the virtual environment was $3^\circ/\text{cm}$. The scaled position of the end effectors was projected onto the computer monitor (53 cm wide and 30 cm high).

The haptic object was represented as a rectangular parallelepiped with the visual appearance of a cardboard box, which indicated to the participant that they were manipulating an object with limited compliance that should be handled with care. Furthermore, to simplify the virtual environment, the orientation of the object was kept fixed throughout the trial (i.e., in an upright orientation) even if the contact forces of the end effectors were misaligned.

The God Object algorithm with friction simulation [195] was chosen to implement the virtual scenario and generate the haptic rendering provided to the partic-

ipants by the wrist devices. In the absence of contact between the end effectors and the haptic object, the wrist robots provided no force and movements were afforded by virtue of the mechanical backdriveable structures. Once the end effectors were in contact with the haptic objects there were main factors that were considered for the implementation of the haptic rendering: the depth of penetration of the end effectors into the parallelepiped, and the different dynamics needed to simulate the interaction with the user. The control scheme is depicted in Fig. 2C and Fig. 2D.

The haptic rendering was evaluated by considering the real positions of the end effectors, the so-called haptic interface points (referred as EE_R and EE_L) and the representation of the end effectors on the screen (i.e., God Objects, GOs), as shown in Fig. 4.2A. In order to generate a haptic force, the distance between the EEs and the GOs along the x-axis was fed back to the controller, and is referred in the following sections as penetration depth (PD). Since the task required that the haptic object was lifted using the two end effectors, static friction was also simulated. Fig. 4.2B depicts the friction cone centered in EE_L , oriented in the normal direction (N) to the contact surface. The friction cone was defined as the intersection between the cone and the surface. Once the GO was outside the friction cone surface (as a consequence of the movement of the EE), the GO was updated to the closest point of this surface (Fig. 4.2C). This highlights that the real positions of the end effectors (EEs) were the ones by which the interaction forces were calculated and fed back to the user, while the GOs were a graphical representation of the end effectors after the contact with the virtual object during manipulation.

The dynamics of the virtual object and its planar trajectory, described by the position vector y , depended on the amount of force applied during manipulation when the end effectors maintained the contact with the object. Its motion was therefore generated as the result of the external forces F_{ext} comprised of the gravity force (Mg), the friction (F_f) and the viscoelastic forces which were applied by the end effectors F_{EE_L} and F_{EE_R} involved in the contact.

$$M \vec{\ddot{y}} = \vec{F}_{ext} = M \vec{g} + \vec{F}_f + \vec{F}_{EE_L} + \vec{F}_{EE_R} \quad (4.1)$$

The haptic rendering to the user was fed back by the devices (in the FE and AA DoFs) and an impedance controller (Fig. 2D) that regulated the interaction force F_{EE} at each end effector according to the following formula:

$$\overrightarrow{F_{EE}} = M\overrightarrow{g} + K\overrightarrow{x} + B\dot{\overrightarrow{x}} \quad (4.2)$$

where K and B indicate the stiffness and damping respectively, and x indicates the PD of the end effector. Forces were then summed and the object's kinematics was computed using a second-order differential equation derived from Newton's second law. The values and gains ($M = 0.5$ kg, $K = 0.8$ N/cm and $B = 0.005$ Ns/cm) were manually set in order to provide a range of haptic rendering compatible with task duration, mitigate muscular fatigue, and to cover a range of torque/forces without saturating the haptic devices.

The static friction F_f was a force generated by considering the normal force applied on the virtual object which depended on the PD and the friction coefficient μ , and served to prevent object slippage when the two end effectors were in contact with the lateral surfaces of the virtual object during the reach and return phases of the movement. The friction force was parallel to the lateral surfaces of the virtual object and its magnitude was obtained according to the formula:

$$|\overrightarrow{F_f}| = \mu|\overrightarrow{F_N}| = \mu K|\overrightarrow{x}| \quad (4.3)$$

The acceleration of the haptic object was double integrated in order to update the velocity and the position and the corresponding kinematics was fed back to the subjects via the visual display. A high friction coefficient was simulated when

Figure 4.2: (A) Representation of the God Object (GO) algorithm in which the actual position of the end effector is indicated as EE and the position shown on the screen is represented as a GO. (B) Generation of the friction cone. The friction force is evaluated by considering the Penetration Depth (PD) of the EE and multiplying it by a friction coefficient. (C) When the end effector is moved, the corresponding position of the GO is updated. Dotted and solid lines represent previous and updated positions, respectively.

Figure 4.3: (A) Each trial consisted of a reach phase and a return phase. (B) There were five target positions that were equally distributed across the workspace. (C) In the No Feedback condition the participant did not receive haptic or visual information regarding end-effector penetration; in the Visual condition, visual (but not haptic) information about object penetration depth was provided to the participant; in the Haptic condition, haptic information (but not visual) about object penetration depth was provided to the participant; in the Haptic+Visual condition, both visual and haptic feedback about the level of force applied to the virtual object by the two end-effectors were provided to the participant.

the object was on the ground to ensure that participants lifted the object from the resting floor rather than dragging it toward the target. This was achieved by multiplying the velocity, obtained by integrating the acceleration in equation 4.1, by a damping coefficient.

The experimental procedure was based on an analogous experiment described in our previous work [196]. Participants sat in front of the bimanual workstation with the computer monitor 80 cm away, and placed their forearms on the supports, holding both robot handles in 30° in adduction and 0° flexion/extension. After visually confirming that the wrist joints aligned with the axis of the wrist robots and making any necessary adjustments, the participants' forearms were secured to the robot devices using Velcro strips.

For each single trial, participants were requested to lift the object and transport it to the target location (reach phase), and successively returning to the initial position (return phase). There were five target positions ($t_1 = -60^\circ$, $t_2 = -30^\circ$, $t_3 = 0^\circ$, $t_4 = 30^\circ$ and $t_5 = 60^\circ$), virtually represented as a semi-transparent parallelepiped, equally spaced from the starting position (15 cm), Fig. 4.3A and 4.3B. A 15 second time constraint was imposed using a countdown timer displayed on the virtual object (i.e., cardboard carton) that indicated the remaining time for task completion. Participants were informed that they had to maintain an appropriate level of contact force with the virtual object throughout the entire task and that

failure to do so would cause the object to break (when too much force is applied, PD equal to 50% of object width) or slip and fall (when too small or asymmetric forces are applied, PD lower than 10% of object width). If the movement was performed successfully the instruction “return the object to the start position” was displayed at the end of the reach phase. However, if the trial exceeded the time limit or the object was broken, slipped and fell, then the texture of the object changed and the instructions specified that the participant should “release the object”, which would automatically return the object to the initial position. An interval of the duration of 1 second separated the end and the beginning of consecutive trials.

Four conditions were tested, and are depicted in Fig. 4.3C:

1. *No Feedback* condition: The participant did not receive haptic or visual information regarding the end effector penetration after the contact between the end effectors and the object surface occurred. Thus, participants had to rely solely on visual information regarding the position of the end effectors on the surface of the object in order to complete the task.
2. *Visual* condition: Contact between the end effectors and the object surface was visually rendered as a deformation of the shapes of the virtual objects representing the end effector as well as their color change. In this condition, haptic feedback was not delivered to the subjects via the wrist devices.
3. *Haptic* condition: While the end effectors were represented as spheres with no deformation (regardless of the exerted forces), haptic information about object penetration depth was provided to the subject. After collision and penetration of the object by the two end effectors, a viscoelastic force feedback was displayed to the participants via the haptic devices. Thus, participants could rely only on haptic information to regulate the dynamic interaction and avoid object breakage.
4. *Haptic+Visual* condition: Contact between the end effectors and the object surfaces was rendered via both haptic and visual information provided as deformation and change in color of the spheres representing the end effectors.

Visual feedback provided during the Visual and Haptic+Visual conditions changed according to the level of exerted forces and therefore object penetration depth.

Specifically, the spheres (the virtual representation of the position of the two end-effectors) flattened against the object surface proportionally to the penetration depth of the end effectors. In addition, the color of the spheres changed in order to provide supplementary information about the level of penetration. The spheres were colored green prior to object contact and represented the optimal range of applied forces (and object penetration) which allowed to lift and carry the object without breaking it. This color was displayed when object penetration did not exceed $1/4$ of the width (4 cm) of the object. When the penetration depth was within $1/4$ and $1/2$ of the total object's width the color of the sphere changed from green to yellow, indicating that a critical amount of force was being applied on the virtual object. When the maximum penetration depth of $1/2$ of the total object's width was exceeded, the spheres changed from yellow to red and resulted in object breakage. When the maximum force was reached the virtual object was represented as a crushed cardboard carton.

The experiment was organized in two sessions, each comprising two feedback conditions. As shown in Table 4.1, participants were randomly assigned to two groups: Haptic 1st and Haptic+Visual 1st. In Session 1, the Haptic 1st group experienced the Haptic condition first followed by the Haptic+Visual condition. In Session 2, the Haptic 1st group first performed the task under the No Feedback condition, followed by the Visual condition. The Haptic+Visual 1st group performed each session in opposite order of feedback presentation: in Session 1, the Haptic+Visual 1st group experienced the Haptic+Visual condition first followed by the Haptic condition. In Session 2, the Haptic+Visual 1st group first performed the task under the Visual condition, followed by the No Feedback condition.

Participants performed 20 practice trials prior to the experimental test blocks to familiarize themselves with the task and the mapping of the wrist interface in

Table 4.1: *Order of feedback presentation for the two groups.*

Group	Session 1		Session 2	
	Condition 1	Condition 2	Condition 1	Condition 2
Haptic 1 st	<i>Haptic</i>	<i>Haptic+Visual</i>	<i>No Feedback</i>	<i>Visual</i>
Haptic+Visual 1 st	<i>Haptic+Visual</i>	<i>Haptic</i>	<i>Visual</i>	<i>No Feedback</i>

the virtual environment. During the familiarization phase, neither haptic nor visual feedback was provided. Participants then took a 2-minute rest break, after which the experiment commenced. Each session consisted of 100 trials (two conditions or target sets of 50 trials), within which the five targets were presented in a random fashion. The experimental sessions were separated by a period of 3 months and lasted approximately forty minutes each.

4.1.2 Data analysis and results

Trajectories of the left (EE_L) and right (EE_R) end effectors, recorded at a sampling frequency of 250 Hz, were filtered using a 6th order Savitzky-Golay filter (11 Hz cut-off frequency). For each trial, data were divided into a reach phase and a return phase. The reach phase was defined as the time between the movement of the parallelepiped was initiated and the moment the object was placed on the target (i.e., object velocity was below a 2 cm/s threshold and the distance to the target center was 0.5 cm). The return phase was defined as the time between when the end effectors left the target and the time the object was placed back on the resting floor (i.e., object velocity was below a 3 cm/s threshold).

We quantified the similarity between dominant and non-dominant wrist (bimanual coordination) by analyzing the end-effector trajectories in the temporal and spatial domains. In particular, the following metrics were analyzed:

Reach Time was defined as the amount of time (s) taken to move the object from the starting position to the target.

Return Time was defined as the amount of time (s) to move the object from the target back to the resting floor.

Dynamical Symmetry Index (DSI) [197] is a modified version of the symmetry index (SI) proposed by Robinson et al. [198] used to evaluate bimanual temporal coordination.

$$DSI(t) = \frac{\Delta X_D(t) - \Delta X_{ND}(t)}{0.5(\Delta X_D(t) + \Delta X_{ND}(t))} \quad (4.4)$$

where $\Delta X_D(t)$ and $\Delta X_{ND}(t)$ are the distances from the initial starting point of the trajectories of the dominant and non-dominant wrist respectively. The magnitude of the index expresses the percentage difference between trajectories of the

two end effectors during the bimanual grasp and reach task. The sign indicates the pattern of asymmetry ranging from $\pm 200\%$, in which positive values indicate that the dominant wrist travels a longer trajectory in the same amount of time than the non-dominant one. Negative signs of the DSI describe an opposite situation in which the non-dominant wrist traces a longer path than the dominant one. A value of 0% reflects perfect symmetry, while the extremes indicate greater asymmetry. Lastly, $|SI| < 10\%$ indicates symmetry, whereas larger values indicate asymmetry.

Discrete Fréchet Distance (DFD), also termed the coupling measure [199,200], is a measure of the similarity between two polygonal curves quantified as the minimum cord-length that connects the two curves as they move toward a target without backtracking.

The trajectories of EE_L and EE_R were considered by setting their initial points as the points of contact with the objects during reach and return phases. The DFD is zero when the two trajectories are equal and grows positively as the curves become more dissimilar.

Bimanual coordination was examined using Repeated Measures Analysis of Variance on the variables Reach Time, Return Time, Discrete Fréchet Distance and mean Dynamical Symmetry Index, with Group (Haptic 1st, Haptic+Visual 1st), Condition (Haptic, Haptic+Visual) and Target (t_1, t_2, t_3, t_4, t_5) as factors. Statistical significance was considered for p -values lower than 0.05. Post-hoc analysis on significant main effects and interaction was performed using Bonferroni-corrected paired t-tests.

Trial Completion

The percentage of trials with errors (i.e., the object was broken due to excessive force or slippage, the trial exceeded the allotted time limit) was similar between groups (32.2% and 31.3% for Haptic 1st and Haptic+Visual 1st respectively), indicating that performance was not influenced by condition presentation order. Exemplar movement trajectories from a single participant in each of the four feedback conditions are depicted in Fig 4.4.

Chi-Square Analysis indicated a significant effect of Condition on the number of failed trials, $\chi^2_{(3)} = 217.68, p < 0.0005$. Overall, the percentage of errors was higher for the No Feedback Conditions (54.7%) compared to Visual (41.3%), Haptic (13.7%) and Haptic+Visual conditions (17.3%), as well as for the Visual condition

Figure 4.4: *Reaching trajectories from a single participant (group Haptic 1st) in each of the four feedback conditions (top: Haptic condition and Haptic+Visual condition, bottom: No feedback condition and Visual condition) across the five different targets. The black line represents the average of the completed reach trials while the shaded area indicates the standard error across all trials.*

compared to the Haptic and Haptic+Visual conditions, both p 's < 0.008 . The difference between Haptic and Haptic+Visual conditions was not significant, $\chi^2 t_{(1)} = 2.60$, $p = 0.107$. The number of trials due to errors was 15.5% in Session 1 (Haptic and Haptic+Visual conditions) and 48% in Session 2 (Visual and No Feedback). Inspection of the data indicated that the major cause of errors was the application of forces on the object that exceeded the limits imposed. Due to the high error rate during the Visual and No Feedback conditions, the detailed analysis was restricted to the Haptic and Haptic+Visual conditions (i.e., feedback conditions in Session 1).

Reach Phase

Average reach time values were similar for the Haptic (3.64 s, 95% CI [3.19-4.08]) and Haptic+Visual conditions (3.82 s, 95% CI [3.36-4.28]), $F_{(1,10)} = 1.245$, $p = 0.291$. There was, however, a main effect of Target, $F_{(4,40)} = 10.088$, $p < 0.001$, with Bonferroni-corrected post-hoc analysis revealing significant shorter values for t_3 (3.23 s, 95% CI [3.0-3.52]) compared to all other targets (mean value: 3.86 s) $p < 0.05$ (Fig. 4.5A). The interaction between Group and Condition was also significant, $F_{(1,10)} = 21.357$, $p < 0.001$, such that longer reach times were recorded during the first feedback condition (Fig. 4.5B). Specifically, reach times for the Haptic+Visual 1st group were significantly longer for the Haptic+Visual condition (4.40 s, 95% CI [3.75-5.05]) compared to the Haptic condition (3.44 s, 95% CI [2.81-4.07]).

Mean Dynamical Symmetry Index values were similar regardless of feedback condition (Haptic = 0.69%, 95% CI [-5.59-6.97], Haptic+Visual = 1.83%, 95% CI [-5.09-8.75]), $F_{(1,10)} = 0.134$, $p = 0.72$ (Fig. 4.6). There was, however, a significant effect of Target ($t_1 = 26.34\%$, 95% CI [16.82-35.87], $t_2 = 17.11\%$, 95% CI [10.12-24.12], $t_3 = 3.45\%$, 95% CI [-4.39-11.30], $t_4 = -13.24\%$, 95% CI [-21.65- -4.83], $t_5 = -27.38\%$, 95% CI [-35.34- -19.42]), $F_{(4,40)} = 53.83$, $p < 0.0005$. Bonferroni-corrected

Figure 4.5: Average reach time values for the two feedback conditions as a function of Target (A) and Group (B).

Figure 4.6: Reach phase Dynamical Symmetry Index averaged across subjects for the five targets in the two feedback conditions.

Figure 4.7: The polar plot illustrates the average reach phase Discrete Fréchet Distance for the factors Condition and Target. The dotted line represents standard errors between participants. The time series graphs indicate the penetration depth (PD) of the two end effectors (EE_L and EE_R) during the Haptic (black lines) and Haptic+Visual (grey lines) conditions. Shaded area represents standard errors between participants.

post-hoc analysis revealed significant differences among all targets combinations except for the targets t_1 and t_2 ($p = 0.07$).

There was a main effect of Condition on Discrete Fréchet Distance, $F_{(1,10)} = 22.27$, $p = 0.001$, with more similar spatial trajectories of EE_L and EE_R during the Haptic+Visual (3.11 cm, 95% CI [2.59-3.62]) compared to the Haptic condition (3.72 cm, 95% CI [3.13-4.31]) (Fig. 4.7). The main effect of target was also significant, $F_{(4,40)} = 7.42$, $p < 0.0005$ (Fig. 4.7). Bonferroni corrected post-hoc analysis revealed significant differences ($p < 0.05$) between t_3 (2.93 cm, 95% CI [2.38-3.48]) and the rightmost targets ($t_4 = 3.81$ cm, 95% CI [3.07-4.56], $t_5 = 3.77$ cm, 95% CI [3.21-4.33], respectively).

Return Phase

Average return time values were similar regardless of the factors Group (Haptic 1st = 3.05 s, 95% CI [2.42-3.69], Haptic+Visual 1st = 3.79 s, 95% CI [3.15-4.42]), $F_{(1,10)} =$

3.37, $p = 0.96$, and Condition (Haptic = 3.25 s, 95% CI [2.70-3.79], Haptic+Visual = 3.59 s, 95% CI [3.15-4.03]), $F_{(1,10)} = 3.22$, $p = 0.103$. There was, however, a significant main effect of Target, $F_{(4,40)} = 10.93$, $p < 0.001$. Although return time values were shorter for movements from t_3 (3.01 s, 95% CI [2.57-3.46]) compared to all other targets, Bonferroni corrected post-hoc analysis revealed that the only statistically significant differences in return time values were between t_3 and t_2 (3.61 s, 95% CI [3.15-4.06]) and t_4 (3.74 s, 95% CI [3.27-4.21]), both p 's < 0.05 (Fig. 4.8A). There was also a significant Group x Condition interaction, $F_{(1,10)} = 6.635$, $p = 0.028$ (Fig. 4.8B). While return time values were similar for the Haptic 1st group regardless of feedback condition (Haptic = 3.12 s, 95% CI [2.36-3.90], Haptic+Visual = 2.97 s, 95% CI [2.35-3.60]), they were significantly longer in the Haptic+Visual condition (4.21 s, 95% CI [3.58-4.83]) than the Haptic condition (3.37 s, 95% CI [2.60-4.14]) for the Haptic+Visual 1st group, $p = 0.001$.

There was a main effect of Target on return phase mean Dynamical Symmetry Index (Fig. 4.9), $F_{(4,40)} = 4.28$, $p = 0.046$. Bonferroni-corrected post hoc analysis revealed significant differences between t_1 and t_4 targets (-9.07%, 95% CI [-18.01- -0.46] and 9.6%, 95% CI [1.66-16.47] respectively) and t_2 and t_5 targets (-9.04%, 95% CI [-17.37- -0.71] and -2.1%, 95% CI [-9.88-5.67] respectively), $p < 0.05$. The interaction between Condition and Target was also significant, $F_{(4,40)} = 5.24$, $p =$

Figure 4.8: Average return time values for the two feedback conditions as a function of Target (A) and Group (B).

0.002. A difference of 22% was found between Group Haptic 1st and Haptic+Visual 1st.

There was a significant main effect of Target on return phase discrete Fréchet distance, $F_{(4,40)} = 4.32$, $p = 0.005$. Bonferroni corrected post-hoc analysis revealed a significant difference between t_2 (2.22 cm, 95% CI [1.68-2.76]) and the rightmost targets ($t_4 = 3.12$ cm, 95% CI [2.71-3.53], $t_5 = 3.05$, 95% CI [2.61-3.50]), $p < 0.05$.

The interaction between Condition and Target was also significant, $F_{(4,40)} = 5.24$, $p = 0.002$ (Figure 4.10). Return phase Discrete Fréchet Distance values were significantly larger for the Haptic condition for targets t_4 and t_5 (mean difference between conditions [Haptic, Haptic+Visual] = 1.13 cm and 0.97 cm respectively), compared to all other targets (mean difference between conditions: $t_1 = 0.28$ cm, $t_2 = 0.12$ cm, $t_3 = 1.02$ cm). In contrast, there was no significant difference in return phase Discrete Fréchet Distance across targets for the Haptic+Visual condition.

4.2 Sensory integration during manipulation and hand specializations

The aim of the present study was to examine interlimb coordination during a dynamically coupled bimanual task in which participants manipulated a virtual object

Figure 4.9: *Return phase Dynamical Symmetry Index averaged across subjects for the five targets in the two feedback conditions.*

Figure 4.10: The polar plot illustrates the average return phase Discrete Fréchet Distance for the factors Condition and Target. The dotted line represents standard errors between participants. The time series graphs indicate the penetration depth (PD) of the two end effectors (EE_L and EE_R) during the Haptic (black lines) and Haptic+Visual (grey lines) conditions. Shaded area represents standard errors between participants.

and were provided with varying haptic and augmented visual feedback about object penetration depth. Results demonstrated that participants were unable to modulate the amount of force exerted on the object (and thus successfully complete the task) in the absence of haptic feedback. Specifically, the number of unsuccessful trials was significantly higher during the No Feedback and Visual conditions (54.7% and 41.3% respectively) compared to the Haptic and Haptic+Visual conditions (13.7% and 17.3% respectively). In the current experiment, the perception and discrimination of object compliance were crucial to task completion. The decrease in performance when only visual feedback was provided is congruent with a prior research by Kuschel et al [201], in which participants compared two stimuli (i.e., a standard stimulus and a comparison stimulus) and decided whether the second stimulus was more compliant than the first one. Kuschel et al reported that compared to when they were provided with haptic and visuohaptic feedback, participants had difficulty in discriminating between stimuli when only visual compliance cues were presented, suggesting that haptic feedback is required for the accurate perception of object compliance during virtual object manipulation tasks.

Contrary to our original hypothesis, performance was not improved when both haptic and visual feedback was provided (i.e., Haptic+Visual condition). In order to perform the task without breaking the virtual object, participants integrated information from different sensory modalities in order to form a coherent percept of the virtual environment. It has been suggested that the interaction between the two sensory inputs may not be based on a simple algebraic sum, and is supported by empirical research revealing different time-period necessary for the two sensory inputs to reach the central nervous system (supported by the different latency of their primary components in the cortical evoked potentials [202–204] or to reach consciousness [205]). Processing input from multiple sensory sources requires more neurocomputational resources, which results in a slow-down of all output processes, and errors related to the necessity to distribute selective attention between the increased number of output channels [206].

This result might also derive from the difference in the variance of the visual and haptic stimuli. Participants’ reliabilities of the bimodal percept seemed to be linked to the appropriateness of the haptic modality (more reliable than the visual modality when presenting compliance information), that presented information about object compliance with a lower span of variability.

Kuschel et al. [201] investigated the hypothesis that visual and haptic cues are fused in a fashion similar to a maximum-likelihood integrator, where visual dominance occurs when the variance associated with visual estimation is lower than that associated with haptic estimation (and vice versa), as demonstrated by Ernst and Banks [190]. Our results did not corroborate that the combined bimodal percept was an average of single-modality percepts, nor was there evidence that sensory information was fused in an optimally weighted fashion as predicted by the maximum-likelihood theory. While the study by Ernst and Banks [190] tested perception and perceptual judgement, our work focused on the effect of the percepts on the motor action.

Contradicting our initial hypotheses that an augmented visual feedback would facilitate task execution, our results indicated that sensory fusion did not occur in the Haptic+Visual condition. Rather, our results suggest that task performance was improved when the combined percept of visual and haptic object compliance was close to the modality carrying the least compliant stimulus (i.e., the Haptic

condition).

Anisotropy across the task workspace

Results indicated that interlimb coordination was influenced by the target position, such that the end effectors exerted different levels of virtual object penetration depending on the position of the target in the workspace. In addition, the observed spatial anisotropy was present in the Haptic but not the Haptic+Visual condition (Fig. 4.7 and Fig. 4.10). In the Haptic+Visual condition, the degree of spatial coordination was similar across the whole workspace. In contrast, the degree of spatial similarity was higher for targets in the left, than the right, workspace during the Haptic condition.

We postulate that the spatial asymmetry arises from the difference between right/dominant and left/non-dominant hand's roles, which clearly influenced the outcomes for the spatial domain. The extensive literature on neuro-developmental research [207, 208] has revealed an asymmetry in the neuromotor system, in which the left hemisphere (dominant) develops earlier than the right hemisphere (non-dominant), and is thought to be the basis for hemispheric specialization of the right and left hands.

In the Haptic condition, the Discrete Fréchet Distance between the two end effectors increased for rightward targets, when the right hand should follow the haptic input from the left hand which is the one leading rightward movements (as shown by the plots on penetration depth in Fig. 4.7 and Fig. 4.10 for reach and return phases respectively). In the condition in which feedback is "purely haptic", the right/dominant hand performs with a reduced spatial coordination (higher Discrete Fréchet Distance values), while in the Haptic+Visual condition (where visual feedback of object penetration is provided) the two hands exhibit higher spatial coordination (lower Discrete Fréchet Distance values) and a high spatial symmetry across the whole workspace and for different targets. The results of the present study suggest that manual asymmetry and role assignment are flexibly and functionally guided by the type of activity, and the demands of the task.

After observing people performing manual tasks in different conditions, Guiard [209] proposed three high-order principles governing the asymmetry of human dynamically coupled movements. First, the non-dominant hand sets the frame of

reference for the action of the dominant hand. The second principle states that the hands act at different temporal and spatial scales and the granularity of action of the non-dominant hand is coarser. Lastly, the sequence of action is non-dominant followed by dominant. Even when we grasp bimanually a single object and opposing identical forces are applied, the brain allocates different functional roles to the hands: one hand stabilizes the object to provide the frame of reference to the other acting hand [210]. The present study builds upon this work and demonstrates that these principles extend to bimanual control of robotic haptic devices.

Temporal coordination depends on trial initial conditions

Although temporal coordination was similar during the Haptic and Haptic+Visual conditions, there were observable differences between the reach and return phase of the task. Results showed that during the reach phase the left/non-dominant hand led the movement for rightward targets (t_4 and t_5 , while the right hand/dominant led the movement for leftward targets (t_1 and t_2).

We may have expected a similar situation for the return phase of the movement, from the target towards the starting position, but surprisingly the Dynamical Symmetry Index showed a negative bias, indicating a movement lead by the non-dominant/left hand. It is likely that this finding is due to the difference between the initial conditions between the reach and return phases. During the reach phase, the virtual object was picked up from the resting floor, which ensured intrinsic stability at the start of the phase. In contrast, the virtual object was in a state of precarious stability at the start of the return phase, subject to gravity, which was compensated by the friction force generated by the penetration depth and the human-generated torque on the haptic devices. Thus, it is postulated that the non-dominant/left hand, usually more devoted to processing haptic interaction, acted to stabilize the bimanual action (prior to movement of the dominant/right hand) in order to compensate for the initial conditions of the return phase.

Our hypothesis is in line with research indicating that the non-dominant limb is more adept at achieving and maintaining a steady state position and preserving manipulation stability [211]. The outcomes are congruent with the work of Guiard [209] and Johansson et al [210] reporting that the lateralization of dominant and non-dominant limbs is beneficial for bimanual tasks. Further support is provided by

the average values of the penetration depth as a function of time. As can be seen in Figure 11, the left/non-dominant hand temporally anticipates the penetration of the virtual object during the return phase, which was present in the majority of the targets. In contrast, during the reach phase, the left and right hands had actions that were temporally distinguishable, with the left hand penetrating with an anticipatory movement during the rightward reach phase, and vice versa for leftward targets.

This study provides new evidence about the role of visual and haptic information on simulated dynamically coupled bimanual manipulation. However, there are several limitations to the current study which may inform future directions in this line of research. First, we limited data collection to right-hand dominant individuals. There is now a large corpus of research demonstrating that the organization of motor cortical representations [212,213] and corpus callosum morphology [214,215] differs between left- and right-handers. For example, a recent study [216] examined the contributions of vision and haptics to hand preference for grasping in left- and right-hand dominant individuals. Results indicated that while left-handers exhibited a consistent left-hand grasp preference regardless of condition, right-hand dominant individuals were less likely to use the right hand to grasp the object when vision was occluded, but more likely to use the right hand when haptics was constrained. On the basis of these results, the authors argued that hand preference during grasping actions is influenced by haptic and visual information as well as hand dominance. These novel findings highlight the need for future research to examine potential differences in manual lateralization and role assignment in presence of visual and haptic feedback in between left- and right-handers, as these might provide illuminating insights into motor system organization.

4.3 Differences between unimanual and bimanual proprioception

There is empirical evidence from both lower and upper limb studies involving both injured and healthy individuals [217,218] that bilateral proprioceptive performance is lowered to the level of the lower performing limb, indicating that when a single limb with higher proprioceptive acuity performs a movement simultaneously with the other limb. The consequence is a decrease in bilateral movement discrimination

performance. Conversely, a recent study [219] has suggested that the central nervous system is aware of and utilizes information obtained by the limb with the best proprioceptive acuity for bimanual judgments.

In order to expand this corpus of work, we report the results of a study examining dominant and non-dominant distal upper limb joint position sense by means of a robotic bimanual wrist device and investigated whether proprioceptive performance differ depending on whether the matching task is performed with one or two hands. It was expected that wrist proprioceptive acuity would be better during unimanual, compared to bimanual, task performance, in line with previous findings demonstrating that bimanual movements take longer to plan [220] and execute than similar unimanual actions [221] [222].

4.3.1 Participants and protocol

The participants described in Section 3.1.1 performed a JPM in the bimanual condition. Participants performed 12 trials per DoF (FE, AA) for a total of 24 trials in each of the 3 task conditions (Unimanual-Right, Unimanual-Left and Bimanual), yielding a total of 72 trials. Trials across DoFs and conditions were presented in a pseudo-random fashion. The experiment lasted approximately 30 minutes.

4.3.2 Data analysis and results

The data collected were analyzed to obtain the proprioceptive acuity in terms of Absolute Error and Variability, and the kinematic metrics Speed and Smoothness. These are described respectively in Equations 2.1, 2.2, 3.1 and 3.2. Data were subjected to a 2 (DoF: FE, AA) x 2 (Hand: left, right) x 2 (Task: unimanual, bimanual) Repeated Measures ANOVA separately for each outcome measure. Results with p values < 0.05 were considered significant. Significant main effects and interactions were compared using the Bonferroni procedure.

Results are reported in terms of mean across subjects $\pm$ SE. The main effect of Task was significant, $F_{(1,216)} = 20.652$, $p < 0.001$, with smaller matching error values during the unimanual ($3.6 \pm 0.2^\circ$) than the bimanual condition ($4.9 \pm 0.2^\circ$). Average matching error values were similar for the left ($4.3 \pm 0.3^\circ$) and right hand ($4.2 \pm 0.2^\circ$), $F_{(1,216)} = 0.49$, $p = 0.83$. There was, however, a main effect of DoF,

Figure 4.11: *Wrist proprioceptive acuity. (A) Matching error, (B) Variability, (C) Speed and (D) Smoothness for the FE and AA DoF in the unimanual (black lines) and bimanual (gray lines) task.*

with movements to AA ($3.8 \pm 0.2^\circ$) yielding smaller matching error values than movements to FE ($4.7 \pm 0.2^\circ$), $F_{(1,216)} = 9.007$, $p = 0.003$. Matching errors for the different tasks in the DoFs are reported in Figure 4.11A. Analysis of variable error are shown in 4.11B. Movements were more consistent during the Unimanual ($2.9 \pm 0.1^\circ$) compared to the Bimanual condition ($3.3 \pm 0.2^\circ$), $F(1,261) = 4.501$, $p < 0.001$. In addition, movements in the AA DoF ($2.5 \pm 0.1^\circ$) were more consistent than those made in the FE DoF ($3.6, \pm 0.1^\circ$), $F_{(1,216)} = 33.237$, $p < 0.001$. Variability values were similar for the left ($3.0 \pm 0.1^\circ$) and right hand ($3.1 \pm 0.1^\circ$), $F > 1.0$.

Figure 4.11C illustrates the wrist Speed during the active matching phase. Average mean speed was significantly higher for Unimanual movements ($70.8 \pm 2^\circ/\text{s}$), compared to Bimanual movements ($63.7 \pm 3^\circ/\text{s}$), $F_{(1,216)} = 7.0682$, $p = 0.0084$. There was also a significant main effect of DoF, with lower mean speed values for AA ($48.5 \pm 1.7^\circ/\text{s}$) than the FE DoF ($86.0 \pm 3.1^\circ/\text{s}$), $F_{(1,216)} = 197.60$, $p < 0.001$. Mean speed values were similar for the left ($65.5 \pm 2.1^\circ/\text{s}$) and right hand ($69.0 \pm 2.5^\circ/\text{s}$), $F > 1.0$. Average movement smoothness, reported in 4.11D, was significantly larger for unimanual movements (0.5 ± 0.05), compared to bimanual movements (0.4 ± 0.05), $F_{(1,216)} = 6.1192$, $p < 0.001$. Furthermore, movements were smoother when performed by the left (0.5 ± 0.04) compared to the right hand (0.3 ± 0.03), $F_{(1,216)} =$

24,974, $p < 0.001$. The main effect of DoF (AA: 0.4 ± 0.02 ; FE: $0.4 = 0.5 \pm 0.03$) was non-significant.

4.4 Bimanual matching decreases proprioceptive performance

The purpose of the current study was to investigate whether proprioceptive performance and movement kinematics differ depending on whether the motor task is performed with one or two hands. We found that proprioceptive acuity and movement kinematics were different in the ipsilateral (unimanual) and contralateral (bimanual) matching task. Results revealed that proprioceptive accuracy was greater and more consistent, and movements were faster during the unimanual than the bimanual condition. However, our data do not support recent findings suggesting that the central nervous system utilizes signals from the limb with the best proprioceptive acuity during bimanual movements [219]. We did not find a significant interaction between hand (left, right) and the task (unimanual, bimanual). Rather, our findings support behavioral motor control research indicating that decreased performance during the execution of bimanual movements arises from callosally mediated mutual inhibition. By this account, bimanual movements result in the transmission of rapid interhemispheric signals from each hemisphere. These signals activate inhibitory networks in the contralateral hemisphere, the end result of which is a slowing of the responses from both hands. The same rapid interhemispheric signals are transmitted during unimanual movements, but only from the responding hemisphere. In contrast to bimanual movements, the inhibitory influence does not affect reaction times as the inhibited hemisphere does not evoke a motor response. The present data suggest that the bimanual cost, often observed during motor execution, can also be found during bimanual proprioception. In addition, we also found that proprioceptive acuity was better and more consistent for the AA than the FE DoF. This anisotropy in proprioceptive acuity might be due to the distribution of receptors in the human wrist joint as discussed in Chapter 2.

A number of neurological disorders (e.g. stroke; Parkinson's disease, peripheral neuropathy) result in sensory deficits and abnormal proprioceptive function, that have a negative influence on postural control, motor coordination, motor learning,

and motor recovery [223]. Thus, the accurate quantification of joint position sense can provide important information regarding the patient’s post-injury status and the efficacy of the therapeutic approaches. At present, there is no established quantitative method for the clinical assessment of proprioception. However, recent advances in haptic interfaces designed for robot-aided sensorimotor rehabilitation may prove useful in the assessment of proprioceptive function [224]. The results of the current study have implications for robotic evaluations of proprioceptive acuity. In consideration of the differences observed for unimanual and bimanual proprioception, it is critical that proprioceptive performance is compared to the results obtained with the same test. Given the differences in proprioceptive acuity between different DoFs, robotic evaluations should gather measures in more than one DoF in order to provide a complete picture of proprioceptive function.

4.5 Summary

The present study demonstrated that the role of the haptic and visual feedback is primarily driven by the lateralization of the dominant and non-dominant hands during a dynamically coupled bimanual task. On the other hand, proprioceptive functions are influenced by the experimental conditions (unimanual or bimanual). Results showed lower matching performance during a contralateral (bimanual) JPM task, while the ipsilateral (unimanual) test resulted in more precise and consistent matching. Despite the fact that movements were found to be faster in the unimanual task, they resulted smoother if performed with two hands at the same time.

Chapter 5

Testing healthy arm and wrist proprioception under clinical limitations

This chapter reports the evaluation of the proprioceptive performance of the healthy arm and wrist by mean of a JPM protocol which, by involving only passive movements, can be used to monitor proprioception of stroke patients with motor impairments.

As introduced in Chapter 3, sources of proprioceptive information employed at different joints may differ, and, while we did not observe a significant asymmetry in the proprioception of the dominant and non-dominant wrist, it can be present at the arm [225]. Moreover, some evidence suggests that proprioception can deteriorate as a result of aging. We have therefore analyzed proprioception of both arms and proprioception of the dominant wrist of healthy subjects of different age and established its acuity, bias, and consistency. Spatial sensitivity of the revised JPM paradigm was also evaluated by detecting differences between these metrics in different movement directions.

Finally, we introduced H-Man as a tool of proprioceptive assessment of joint position sense of the arm and we gather normative data for future studies on both arm and wrist proprioception with stroke patients.

Part of the results presented in this chapter can be found in [226].

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Juergen Konczak and Lorenzo Masia, A preliminary study for quantitative assessment of upper limb proprioception, Engineering in Medicine and Biology Society (EMBC), 2016 38th Annual International Conference of the IEEE, 2016.

5.1 Refined paradigm for testing arm proprioception

The joint position matching test presented in Chapter 2 has been shown to be effective in the assessment of changes in proprioceptive acuity [35]. Unfortunately, this method has practical implementation issues such as time constraints, equipment required and cost, and, to date, it has not been established as gold standard in clinical settings.

We propose a refined method for proprioception assessment with the aim of satisfying the requirements of clinical implementation: accuracy and reliability but also ease of use and quickness. In order to fulfill the requirement of accuracy and reliability, the implementation of a protocol employing a robotic device has been chosen. Contemporary robotic devices have the proven capability to accurately manipulate joint movements. In addition, they provide high-intensity, repetitive, task-specific, and interactive environment to enhance motor learning of the impaired upper limb and objective and reliable tools for the assessment of patient progress [63]. However, robotic devices are often too complex for everyday clinical practice. For this reason, and for fulfilling the requirement of ease of use, in addition to the Wrist robot, we chose H-Man, a novel low-cost planar robot designed for neurorehabilitation of sensorimotor functions. Its simple design is ideal for rehabilitation in decentralized environments, such as patient's home, or in small clinics. The same robotic device can be used for motor assessment and training of sensorimotor functions, hence limiting the need for additional equipment for rehabilitation protocols.

Further, the use of these robots allows the administration of a JPM paradigm to assess the accuracy of passive joint-angle replication. While active target replication involves a voluntary movement of the participant's limb to a predefined position, passive movements can be performed with the help of such robots in order to test proprioception of patients with a range of motion impaired by neurological diseases. With regard to the requirement of quickness, the approach proposed in this chapter

limits the test time duration to around 10 minutes, such that it can be integrated as a part of other motor and sensory assessments.

In the following sections, we present the methodology and the results obtained with the refined JPM protocol with the aim to create a database of proprioceptive acuity to form a baseline for comparisons with stroke patients. To this end, we took into consideration the variability in stroke characteristics, which are highly variable and can affect the measured metrics. In fact, the side of the lesion can interest both the dominant and the non-dominant side of the body, with some studies providing evidence for a higher incidence of left-hemispheric strokes, resulting in a worse outcome than their right-hemispheric counterparts [227–229], asymmetry probably related to the fact that left-sided strokes seem more easily recognizable [230]. Moreover, stroke can happen at any age, with recent studies presenting evidence of a significant decrement of mean age at stroke and an increment of stroke incidence rate in patients under age 55 [231].

We have therefore analyzed the matching performance of healthy subjects and evaluated the effect of such properties, i.e. age and handedness, on the normal range of acuity. We also account for differences in movements in everyday life which require a different degree of interaction between the shoulder and elbow joints by evaluating spatial sensitivity in arm proprioception.

5.1.1 Participants and assessment protocol

A total of 23 participants were recruited for the study. Twelve healthy participants were grouped according to their age. Six participants (2 females), whose age was in the range 24 - 29 (mean = 27.3) years were assigned to the Young group while the remaining six (4 females), who had an age in the range 46 - 56 (mean = 53.5) years formed the Aged group. These participants were right-handed and had no reported neurological, psychiatric, or neuromuscular disorders.

Another group of 11 healthy subjects (9 males, 2 left-handed, mean age $\pm$ SD: 26.6 $\pm$ 4.7 years old) performed the experiment with both arms to determine the effect of handedness on arm proprioception. All healthy participants were naive to the purpose of the experiment and provided informed consent prior to participation in the study.

Participants sat in front of the robotic device such that their sternum was initially

Figure 5.1: *Experimental procedure. The participants' hand was moved by the device to one of three possible targets. The matching error was considered as the difference between the current target and perceived target positions, verbally indicated by the subject.*

aligned with its handle, and the elbow was bent at approximately 90° . The position of the handle in the resting position was set to ~ 20 cm in front of the midline of the body (Figure 5.1). Participants were instructed to face forward, to maintain their eyes closed for the duration of the experiment (they were blindfolded when requested) and to keep their arm muscles relaxed, restraining from applying any force to resist the movement of the handle for the whole duration of the experiment. No feedback about their performance was provided between trials to avoid recalibration.

Three target positions at a fixed distance of 10 cm from the initial position were selected in the forward and oblique directions in the contralateral and ipsilateral sides of the tested arm (angles: -45° , 0° , $+45^\circ$) for passive assessment of joint position sense. Targets are called, respectively, contralateral, central, and ipsilateral when testing the right arm, while, for the left arm, contralateral and ipsilateral refer to the target at an angle of $+45^\circ$ and -45° respectively.

In order to measure the ability to match the perceived position to a predefined target, the participant's limb was passively moved by H-Man at a velocity of 7 cm/s

to one pseudo-randomly selected target position (Criterion movement) and held there for 2 seconds to allow participants to memorize the position. The limb was then returned to the starting position, and, after a dwell time of 1 sec, the Matching movement towards the same target was initiated by H-Man, this time at a velocity of 2 cm/s. Participants were instructed to verbally indicate when the handle position matched the target position, at which point the experimenter stopped the handle movement via a programmed button. The handle was then returned by the robot to the initial position at a velocity of 7 cm/s for the beginning of the subsequent trial.

The lower velocity of the Matching movement was selected to avoid reliance on the movement duration for determining target position and to ensure negligible variation in position due to the delay between the verbal instruction from the participant and the moment the experimenter presses the button to stop the movement.

The test comprised a total of 30 trials with 10 trials in each direction. To avoid any decline in concentration and drift in the proprioceptive sense, a 3-minute break was provided after completion of half of the experiment, which had a total duration of approximately 10 minutes.

5.1.2 Analysis and results

The limb proprioceptive acuity, positional bias and the consistency of position matching were respectively characterized in terms of Absolute error (Equation 2.1), Signed error (Equation 3.3) and Variability (Equation 2.2).

Statistical quantification of the differences related to age, handedness and target position was conducted. Results from the participants divided into age groups were submitted to a One-way ANOVA with factor Group (i.e. Aged, Young). Similarly, data recorded from participants testing both the dominant and non-dominant side were analyzed with a Repeated Measures ANOVA with factor Hand. Finally, data from all participants related to the dominant arm were pooled to evaluate the effect of Target by mean of a Repeated Measures ANOVA with factor Hand. Preliminary analyses were conducted to check for normality (Shapiro Wilks test), sphericity (Mauchly test) and outliers. Correction in case of violations of sphericity was performed with the Greenhouse–Geisser method. Results with p-values <0.05 were considered significant. Significant main effects and interactions were compared

Table 5.1: *Mean $\pm$ SD for the different factors.*

Factor		Absolute Error [cm]	Signed Error [cm]	Error Variability [cm]
Age	Aged	1.18 $\pm$ 0.15	0.82 $\pm$ 0.29	0.83 $\pm$ 0.13
	Young	1.37 $\pm$ 0.35	0.96 $\pm$ 0.59	0.99 $\pm$ 0.27
Hand	Dominant	1.05 $\pm$ 0.47	0.74 $\pm$ 0.67	0.88 $\pm$ 0.34
	Non-Dominant	1.15 $\pm$ 0.45	0.48 $\pm$ 0.98	0.98 $\pm$ 0.21
Target	Contralateral	1.01 $\pm$ 0.55	0.59 $\pm$ 0.85	0.81 $\pm$ 0.27
	Central	1.16 $\pm$ 0.46	0.81 $\pm$ 0.77	0.94 $\pm$ 0.56
	Ipsilateral	1.34 $\pm$ 0.54	1.05 $\pm$ 0.80	0.93 $\pm$ 0.39

Figure 5.2: *Mean $\pm$ SEM of Absolute error, Signed error and Variability for the three target locations in (A) Aged (black circles) and Young group (gray circles) and (B) Dominant (black triangle) and Non-dominant arm (gray triangles).*

using Bonferroni corrected post-hoc analysis.

Mean values for the metrics evaluated and their SD are reported in Table 5.1. There were no significant differences between the two groups in terms of Absolute errors, $F_{(1,10)} = 0.45$, $p = 0.52$, Signed errors, $F_{(1,10)} = 0.09$, $p = 0.78$, and Variability, $F_{(1,10)} = 0.65$, $p = 0.44$, as shown respectively in Figure 5.2A, 5.2B and 5.2C.

Similarly to the previous analysis, the statistical test did not detect any significant effect of factor Hand for the three metrics. The statistics were $F_{(1,10)} = 1.19$, p

= 0.30 for Absolute errors, $F_{(1,10)} = 1.37$, $p = 0.27$ for Signed errors, and $F_{(1,10)} = 2.40$, $p = 0.15$ for Variability.

The difference between Absolute errors among the three test locations was significant, $F_{(2,44)} = 9.45$, $p = 0.006$. Participants were significantly more accurate in terms of Absolute error when matching the Contralateral target compared to the Ipsilateral, as revealed by the post-hoc analysis ($p < 0.05$). An effect of Target location was also found significant for Signed errors ($F_{(2,44)} = 5.24$, $p = 0.009$), and, as for the Absolute error, Bonferroni corrected post-hoc analysis revealed a significant difference between Contralateral and Ipsilateral targets ($p = 0.01$). On the contrary, error Variability did not significantly vary across directions (Greenhouse–Geisser corrected: $F_{(1.33,44)} = 0.73$, $p = 0.49$).

5.2 Proprioception of the healthy arm is not affected by age and handedness but is direction dependent

The baseline range of proprioceptive acuity of the dominant arm, bias and consistency were obtained for healthy young and aged participants. Data from the dominant and non-dominant arm were analyzed and the interaction between shoulder and elbow in relation to the movement direction was investigated. The normative data collected were used to evaluate the normal range of arm position sense.

Analysis of signed error showed a general tendency to undershoot the target position, which was not affected by age, handedness and target position. Similarly, matching performance was consistent across trials, as reported by the variable error. The statistical analysis confirmed that also this metric was not affected by the considered factors. Perception of any aspect of movement is based on a mixture of different cues, including information related to time, location, distance and velocity [232]. It is possible that despite the fact that participants were instructed to focus on the final limb configuration, neglecting movement duration, the different movement kinematics biased the participant performance. Participants could have undershot the target to replicate the duration of the faster criterion movement.

We found no decrease in proprioceptive acuity with age in the range analyzed.

Previous studies reported deterioration of limb position sense with age [233, 234]. However, the difference in methodologies employed to test proprioceptive acuity could explain such result: contrarily to the studies from the groups of Adamo and Stelmach, which implemented an active limb matching tasks that involved both arms, our study involved only passive movements towards a previously experienced position. Moreover, the participants in the Aged group had a lower mean age compared to the previous studies, hence less age-related deficits.

We observed significant differences across directions, with smaller absolute and signed error for the contralateral target. Several studies reported a not uniform proprioceptive acuity across the workspace, with greater accuracy in the estimation of hand positions closer to the body due to the larger total changes in joint angle associated with hand movements in this area [235]. In a review by Goble [94], the author reported matching errors measured for right-handed healthy subjects when matching targets in the right or left workspace. The study found a better performance when matching positions in the left of the body midline (contralateral), especially in the far-left workspace. Also, the study of Haggard et al. revealed a contralateral advantage in matching task for right-handed participants, with smaller matching errors for positions in the extreme-left workspace [236].

A possible explanation for this is that movements towards contralateral and central targets require the coordinated rotation of shoulder and elbow joints, while for the ipsilateral target, single joint movements of either shoulder or elbow joints are required [237]. The stretch of muscle spindles is directly related to joint angle change [235] and while signals from two joints are combined when perceiving movements towards central and contralateral targets, movements toward the ipsilateral side are mainly signaled from the rotation of one joint. Moreover, movements toward the contralateral target caused the shoulder to approach the limit of movement, causing tension in muscles, capsuloligamentous structures, and skin. The passive stretch of muscles near the end of the ROM could increase the number of firing muscle spindles resulting in the improvement of the position sense acuity [238]. Indeed, it has been demonstrated that joint position sense is more accurate near the end of the ROM of the shoulder [238] and the wrist [239], where there are more tension and restraints of motion. Finally, the shoulder appears to be more accurate in sensing joint angles compared to distal components [240], and movements towards

the contralateral target required a higher contribution of shoulder motion. Ipsilateral target reaching, on the other hand, involved mainly rotation at the elbow joint, which has a lower proprioceptive acuity, potentially resulting in greater matching errors.

5.3 Passive JPM paradigm for wrist proprioception

As described in the previous sections, the JPM task has implementation issues in clinics that can be overcome with a passive JPM method, while the threshold hunting methods to obtain the JND of wrist proprioception are too time-consuming to be integrated regularly into the conventional clinical assessments.

It is known that the reproduction of a joint position is more accurate when the position is encoded by active movements, which are the predominant movements observed during daily living [241, 242], compared with passive movements. However, active motions may rely on central motor programs rather than a memory of proprioceptive coordinates [243], and the validity of active reproduction is reduced for stroke patients with limited motor functions. In the rest of this chapter, we present a study employing the revised JPM to determine wrist proprioception of healthy participants, which form the baseline necessary to detect deficits in the stroke population.

The preliminary results are analyzed to verify the similarity between matching performance measured with the JPM test presented in Chapter 2 and the revised JPM which only include passive movements. To this end, eight healthy participants performed the passive JPM task with the Wrist robot in six movement directions. The studies presented in Chapter 2, by employing two different tests, revealed an anisotropy across DoFs in both passive and active proprioception. Therefore, the effect of movement direction and DoF were evaluated to further validate the proposed methodology. Finally, we show preliminary results regarding the comparison of the performance of the healthy young subjects to the ones measured from a group of five healthy older participants in order to test whether the similarity between arm proprioception in the different age groups discussed in the previous sections extends to the wrist joint.

5.3.1 Participants and assessment protocol

A total of 13 participants were recruited for the study: eight participants (4 females), whose age was in the range 21 - 33 (mean = 27.2) years formed the Young group while the remaining five (2 females), who had an age in the range 43 - 58 (mean = 55) years were included the Aged group. All individuals in the Young group were right-handed, while one of the five participants in the Aged group was left-handed as confirmed by the Edinburgh Handedness Questionnaire. Both groups had no reported neurological, psychiatric, or neuromuscular disorders.

Participants sat next to the robotic device as described in Section 2.1.1. They were instructed to face forward, to maintain their eyes closed for the duration of the experiment, or they were blindfolded if requested, and to keep their arm muscles relaxed. They underwent the passive JPM task with target positions at the following fixed angles from the initial position: $\pm 30^\circ$ for FE, $\pm 20^\circ$ for AA and $\pm 30^\circ$ for PS. Their dominant wrist was passively moved by the Wrist robot at a velocity of $8^\circ/\text{s}$ to one of the target positions (Criterion movement) and held there for 2 seconds, after which it was returned to the initial position. After a dwell time of 1 sec, the Matching movement towards the same target was initiated by the robot at a velocity of $5^\circ/\text{s}$. Participants were instructed to press a hand-held button when the wrist position matched the target one, after which the handle was returned by the robot to the initial position before a new trial could start.

The experiment consisted of 36 trials with 6 trials in each direction. Targets were presented in the following order: Flexion, Extension, Abduction, Adduction, Pronation, Supination (1 target set). After two target sets, a 1-minute break was provided to avoid drift in the proprioceptive sense. The total duration of the experiment was ~ 10 minutes.

5.3.2 Analysis and results

The wrist proprioceptive acuity was measured in terms of Absolute error, Signed error, and Variability. Due to the limited number of trials, in order to limit the influence of outlying values, the median across trials was used instead of the mean as measures of absolute and signed error. After preliminary analyses of ANOVA assumptions, data recorded from the Young group in the FE and AA DoFs were

Figure 5.3: (A) Absolute errors for the two tests, JPM (black) and revised JPM (gray): small circles represent the errors recorded for each subject across repetitions, while the bigger circles are the mean values across subjects in each direction; (B) Mean and SEM for Variability in the different directions for the two tests, JPM (black) and revised JPM (gray); (C) Mean and SEM for Absolute error and Variability for the Aged (black circles) and Young (gray circles) groups; (D) Mean and SEM for Absolute errors among data from all the 12 participants analyzed.

compared to the data reported in Section 2.1.2 obtained from 14 subjects in the same age range (mean = 26.9). Data were submitted to a mixed ANOVA with between-factor Task (JPM, revisedJPM) and within-factor Movement (Flexion, Extension, Abduction, Adduction) to verify the similarity between results obtained with the two approaches. Further, the complete dataset comprising the PS DoF and data from both groups undergoing the revised JPM task was analyzed to evaluate the effect of target position by mean of a mixed design ANOVA with factors Group (Aged, Young) and Movement (Flexion, Extension, Abduction, Adduction, Pronation, Supination). Results with p-values <0.05 were considered significant and were submitted to Bonferroni corrected post-hoc analyses.

Data analysis revealed that one subject among the young group could not correctly perform the task, probably due to a misunderstanding of the task instructions.

Indeed, the analysis of errors for Subject 5 revealed variability values of 16.2° and 12.3° for FE, 9.1° and 8.5° for AA and 8.2° and 5.6° for PS. Data from this participant were therefore excluded from further analysis.

Absolute errors and mean across subjects are shown in Figure 5.3A. Mean absolute error across all movements obtained by mean of the passive JPM task was $3.03 \pm 0.39^\circ$, which resulted not significantly different from the result of the active JPM ($3.61 \pm 0.28^\circ$), as confirmed by the statistical analysis, $F_{(1,19)} = 1.45$ $p = 0.24$. Mean variability was $2.97 \pm 0.24^\circ$, which closely matched the values obtained by the active JPM task ($2.90 \pm 0.17^\circ$), $F_{(1,10)} = 0.06$, $p = 0.81$. Variability values measured in the two tasks for each movement are shown in Figure 5.3B. An effect of movement direction was found only for Variability, $F_{(3,57)} = 3.76$, $p = 0.02$, and was further analyzed for the revised JPM task by pooling the data from subjects in the two groups, which were found to have similar performance despite the difference in age in all the metrics evaluated (Absolute error $F_{(1,10)} = 0.61$, $p = 0.45$, Signed error $F_{(1,10)} = 0.41$, $p = 0.54$, Variability $F_{(1,10)} = 0.01$, $p = 0.94$), Figure 5.3C.

The difference between Absolute errors among the six directions was significant, $F_{(5,50)} = 3.38$, $p = 0.01$. Pairwise comparisons revealed a significant difference between errors in Flexion and Abduction ($p = 0.04$), and the analysis of DoF revealed that the greatest difference between DoFs was found between the AA ($2.99 \pm 1.21^\circ$) and PS ($4.50 \pm 1.70^\circ$) DoFs, as shown in Figure 5.3D, which however did not quite reach significance ($p = 0.07$). Mean absolute error was $3.64 \pm 1.45^\circ$ for FE.

Similarly, a significant effect of Movement was found for the Signed errors, $F_{(5,50)} = 5.02$, $p = 0.001$, with significant difference between movements in Extension and Pronation ($p = 0.01$). The analysis of the separate DoFs showed a significant difference between the PS DoF ($-2.62 \pm 3.37^\circ$) and both FE ($-0.35 \pm 3.64^\circ$) and AA ($-0.31 \pm 2.94^\circ$), both p 's < 0.01 .

No differences associated to Movement were found for the Variability metric, $F_{(5,50)} = 0.96$, $p = 0.45$. Mean values $\pm$ SD were $3.14 \pm 1.02^\circ$, $2.57 \pm 0.65^\circ$ and $2.49 \pm 1.23^\circ$ respectively for FE, AA and PS.

5.4 Validity of the proposed method evaluated at the wrist

The goal of this preliminary study was to establish proprioceptive performances of healthy subjects by mean of a revised JPM task and to further corroborate the validity of such approach before its application in clinical environments. Indeed, the data gathered are the initial components of a database that will form the baseline measurements for applications with stroke patients. In order to further validate the methodology, we evaluated the capability of the passive JPM protocol to discriminate the different DoFs, which are differently innervated and have different proprioceptive acuities (see Chapter 2). Therefore, we evaluated the effect of movement direction on the matching errors and variability. Finally, the preliminary data collected from two groups of healthy participants of different age were compared, where the age of the Aged group was chosen to match the stroke patients' one.

The active JPM and the revised JPM which employ only passive movements have produced similar results in terms of Absolute errors and Variability, which provide the first evidence of the validity of the method. We also observed significant differences across directions in terms of Absolute and Signed errors, with smaller errors found in the AA DoF, which is an outcome widely discussed in the previous chapters that can be attributed to the higher density of receptors in the ligaments involved in these movements [17, 104].

Similar to the arm proprioception, we found no significant changes in proprioceptive acuity as a result of aging. Again, the difference between our preliminary results and previous studies on the effect of aging on proprioception can be related to the differences between our task and the methodology employed in the literature [233, 234].

A limitation of this preliminary study is the difference in targets chosen for the two JPM tasks. The target positions selected in the studies employing the active JPM were set at 32° in FE and 16° in AA, while the target positions for the revised JPM were set respectively to 30° and 20° . While this difference could have resulted in different performances, it should be considered that the new targets are still far from the limits of the ROM in which different inputs form the proprioceptive information sent to the CNS for conscious perception of joint position. In fact, while the

physiological composition of muscle spindles allows to be sensitive throughout the whole ROM [244], capsular afferents seem to respond only during movements close to the limit of the range of motion, adding information to the signal continuously generated by the muscle spindles [1].

Another limitation is the small sample size. In future, the database will be integrated with data from a larger cohort of subjects, which will include older participants. These data might assist in providing more precise information about the relationship between age and proprioceptive acuity.

5.5 Summary

Measures of proprioception have been recently developed in the research context to allow for precise, accurate, and reliable assessments able to single out the influence of other factors on the outcome. Despite these qualities, the clinical applicability of the protocols is usually limited by different factors, including the equipment required, the technical expertise and time required for the tests administration. In particular, the psychometric method described in Chapter 2 has high sensitivity but requires a considerable administration time for a single limb joint, which is impractical and limits its applicability in clinics. On the opposite side, current clinical tests display limited sensitivity as a result of their ordinal nature and have produced a wide range of contrasting results.

This chapter has presented a measure of joint position sense based on integrated sensors for high precision assessment which can be more easily translated into clinical practice. In conjunction with the ease of use and short time required for the complete assessment of the upper limb and wrist, the protocol has the benefit of employing the same devices for both robotic assessment and motor rehabilitation of arm or wrist. The control data presented have been used to estimate the effect of age, handedness and movement direction on joint position sense of the upper limb. The comparison with the results from the active JPM task provides evidence in support of the validity of the method and its capability to discriminate between DoFs of the wrist and movement direction of the arm. Finally, the preliminary results suggest a limited effect of the age on matching performances in the range analyzed.

The results presented in this chapter will be used in the next chapter as baseline

for determining how stroke influence proprioception of the arm in the chronic stage and proprioception of the wrist in the acute stage.

Chapter 6

Arm and wrist proprioception after stroke

Despite the recognized fact that proprioception is a critical component for motor functions and directly affect motor learning after neurological injuries, clinical tests of joint position sense still lack sensitivity. As seen in Chapter 2, robotic devices, on the other hand, can provide quantitative, accurate, and reliable metrics.

This chapter presents the analysis of the clinical applicability and validity of using robotic devices to quantitatively assess proprioceptive deficits in post-stroke participants. Clinical utility of the proposed methodology and instrumentation was assessed in terms of population who can be screened and time efficiency. Validity was verified in terms of robustness of proposed approach to differentiate between healthy and stroke participants and its relation to task dependence.

Part of the results presented in this chapter can be found in [245].

6.1 Arm proprioception in chronic stroke patients

Proprioception is a critical component for motor control and learning and allows the generation of smooth and coordinated movements [34]. Stroke patients presenting defective proprioceptive abilities may have difficulties in estimating the position of their limbs and maintaining them in a steady posture in absence of vision [27], resulting in negative implications for safety [32] leading to a deterioration of their quality of life. This results in difficulties in learning novel movements, and difficulties in improving the quality of movements over time with functional repetitions [35].

Conventionally used clinical scales for assessment of proprioception are generally ordinal in nature and do not provide a clear distinction between different subcomponents of proprioception. As a consequence, contrasting results have been obtained in the quantification of proprioceptive deficits in stroke patients.

In order to develop a better understanding of proprioceptive defects and their impact on motor functions, different quantitative assessment routines have been proposed in recent years using technological solutions. These paradigms quantify proprioceptive deficits based on movement detection [246–248], discrimination [249] and position matching [82, 94]. In this chapter, we focus on the latter, i.e. position matching, which has been shown to be an effective approach for assessment of change in proprioceptive acuity [35]. However, due to practical implementation issues including time constraints, equipment required and cost, it is yet to be established in clinical settings with stroke participants.

As a step in this direction, we investigate the clinical applicability and validity of the joint matching task presented in Chapter 5 to quantitatively assess proprioceptive deficits in post-stroke participants, keeping in consideration the practical limitations of clinical settings. We selected the passive joint matching approach, designed to analyze the ability to match the passive distance traveled by the limb to account for limited motor functions of stroke patients [250]. Also in this study, the time duration of the complete assessment was set to around 10 minutes, such that it can be integrated as a part of other motor and sensory assessments.

6.1.1 Participants and procedure

Nine stroke survivors (5 males, mean age $\pm$ SD: 53.7 $\pm$ 7.3 years), recruited for a randomized control trial (ClinicalTrials.gov ID: NCT02188628), consented to undergo the proprioceptive test during the week 0 (baseline) motor assessment. The goal of the randomized control trial was to compare differences in clinical outcomes at pre and post-treatment of patients undergoing 1.5 hours of conventional therapy versus one hour of robotic training followed by 30 minutes of conventional therapy. Recruitment was conducted over a period of about 10 weeks (starting from 1st of July 2016 to 9th September 2016). Patients who were screened for eligibility were those under the care of the Rehabilitation Department of Tan Tock Seng Hospital, Singapore. A total of 12 patients were invited for screening and nine met the

Table 6.1: *Chronic stroke patients characteristics.*

Subject ID	Age (years)	Gender	Handedness	Time since onset (months)	Nature (Haemorrhagic or Ischaemic)	Paretic Arm	FMA (0-66)
S1	52	F	R	24	H	R	43
S2	67	M	R	24	I	R	56
S3	56	M	R	7	I	L	40
S4	53	F	L	15	H	L	53
S5	57	F	R	27	H	R	37
S6	42	M	R	17	H	R	56
S7	45	M	R	8	H	R	26
S8	54	F	R	8	H	R	54
S9	58	M	R	7	H	R	31

following inclusion criteria for participating in the study: (1) diagnosis of a single stroke (ischaemic or haemorrhagic) confirmed by brain imaging; (2) post-stroke duration above 3 months; (3) age between 21 and 85 years; (4) hemiplegic pattern of arm motor impairment with shoulder abduction motor power $\geq 3/5$ and elbow flexion motor power $\geq 3/5$ measured with the Medical Research Council (MRC) Scale for Muscle Strength; (5) Fugl-Meyer, arm section (FMA) motor subscore above 20 and (6) presence of motor incoordination or motor ataxia. Patients were excluded if they exhibited cognitive impairments or uncontrolled behavior (Folstein mini mental state exam MMSE $<26/30$). As reported in Table 6.1, two patients had a history of right-hemisphere stroke while the others had left-hemisphere damage and the FMA score of all participants ranged between 22 and 58 (mean value $\pm$ SD: 43.4 ± 13.1). Prior to recruitment, patients signed the informed consent form which conformed to the ethical standards expressed in the 1964 Declaration of Helsinki. The study methodology was approved by the Domain Specific Review Board of the National Healthcare Group (NHG).

The procedure has been adapted from the one described in Paragraph 5.1.1. Participants were seated in a height-adjustable chair in front of the robotic manipulator so that the center of the sternum was aligned with the handle of the H-Man robot. The distance between the initial position of the handle and the sternum was set to 25 cm. The participants elbow was initially bent at approximately 90° and their impaired wrist (or dominant in case of healthy participants) was placed on the handle in a comfortable position. To avoid compensatory movements of stroke patients, shoulder straps attached to the chair were used to maintain their trunk in a static position, while allowing rotation of the shoulder and elbow joints. Stroke

patients hand was strapped to the handle if proper grasp was not possible. All participants were instructed to face forward and to keep their eyes closed (or if requested were blindfolded) and were asked to keep the arm muscles relaxed during the whole duration of the experiment.

To measure the ability to match the perceived position to a predefined target, the participant's limb was moved during the Criterion and then Matching movement by the robot at a velocity of 7 and 2 cm/s respectively towards a target placed at a distance of 10 cm along the forward and oblique directions. We again refer to the targets as contralateral, central, ipsilateral targets, respectively placed at an angle of -45° , 0° , $+45^\circ$ with respect to the frontal plane. The complete assessment consisted of 30 trials, 10 in each direction for the control group and 18 trials, 6 in each direction, for the stroke group. Again, no feedback about matching performance was given during the experiment.

6.1.2 Data analysis and results

Three task performance metrics adopted were Absolute error, Signed error and Variability. Due to the lower number of trials for the stroke population, we consider the median across trials as the measure of absolute and signed error in order to limit the influence of outlying values.

To test the clinical applicability of the proposed methodology, we analyzed differences between control and stroke group using a mixed ANOVA (between-subject factor Group: control and stroke, within-subject factor Target: contralateral, central, ipsilateral) on the group data for absolute and signed errors and variability. Statistical significance was considered for p -values lower than 0.05. Post-hoc analysis on significant effects was performed using Bonferroni-corrected paired t-tests. To evaluate the validity of the proposed methodology for the detection of proprioceptive impairments, pairwise comparisons, with the significance level adjusted (p -values lower than 0.0056), were run between each stroke participant's absolute errors in the 6 trials and the 9 absolute errors of the control group in each direction. Pairwise comparisons were also run between each stroke participant's signed errors in the 6 trials and the 9 signed errors of the control group in each direction.

Figure 6.1: (A) Box-plot of absolute errors for the two groups. (B) Mean absolute errors in the 3 directions for the two groups, where the gray squares represent data from the control group and black circles represent stroke patients. (C) Absolute errors for each patient and mean value of the control subjects.

Absolute errors

Overall, the mean absolute error of the control group (mean value $\pm$ SEM: 1.5 ± 0.1 cm) was smaller and not significantly different from that of stroke patients (1.8 ± 0.3 cm), $F_{(1,16)} = 0.51$, $p = 0.49$ (Figure 6.1A). Analysis revealed a significant effect of Target on the absolute error, Greenhouse-Geisser corrected $F_{(1.28,20.45)} = 5.60$, $p = 0.02$. No interaction effect between Group and Target was found, $F_{(1.28,20.55)} = 0.88$, $p = 0.39$: regardless of the group, the contralateral target was matched with the highest accuracy, with an error of 1.2 ± 0.4 cm and 1.6 ± 0.4 cm for control and stroke group respectively. The central target was matched with a mean error of 1.6 ± 0.3 cm (control group) and 1.7 ± 0.3 cm (stroke group), while the highest error was found for the ipsilateral target: 1.7 ± 0.4 cm and 2.2 ± 0.4 cm. In all cases, the mean absolute control error tended to be smaller than stroke participants (but was not significant). Post-hoc analysis revealed a significant difference between the central and contralateral (mean difference $\pm$ SEM = 0.2 ± 0.1 cm, $p = 0.04$), and between contralateral and ipsilateral (mean difference $\pm$ SEM = 0.5 ± 0.2 cm, $p = 0.03$) as shown in Figure 6.1B.

Analysis of differences between individual stroke participants and the control group showed that two participants, S2 and S4, were significantly different from the control group (Figure 6.1C). Mean differences between control and subjects are reported in Table 6.2, showing significant higher errors for the contralateral and ipsilateral targets for patient S4 and for the contralateral and central targets for patient S2.

Table 6.2: *Pairwise comparisons of Absolute errors between each subject and the control group in the 3 directions. Mean differences are evaluated as Control-S. Significant differences are marked with an asterisk.*

	Contralateral		Central		Ipsilateral	
S	Mean Difference	p-value	Mean Difference	p-value	Mean Difference	p-value
1	0.1	0.76	0.6	0.34	0.3	0.64
2	-3.0	<0.005*	-2.6	<0.005*	-2.1	0.01
3	0.6	0.14	-0.2	0.73	-0.3	0.66
4	-1.4	<0.005*	-1.0	0.10	-2.9	<0.005*
5	0.8	0.03	0.4	0.54	0.4	0.56
6	-0.2	0.64	-0.1	0.88	-0.6	0.42
7	-0.7	0.07	-0.5	0.35	-0.1	0.90
8	0.9	0.02	0.8	0.16	1.1	0.15
9	0.3	0.36	0.3	0.56	-0.1	0.94

Figure 6.2: (A) *Box-plot of signed errors for the two groups. (B) Mean signed errors in the 3 directions for the two groups, where the gray squares represent data from the control group and black circles represent stroke patients. (C) Signed errors for each patient and mean value of the control subjects.*

Signed errors

Control participants reported an average signed error of 1.2 ± 0.2 cm, while the average error for stroke patients was 0.5 ± 0.4 cm, indicating a higher tendency of undershooting for control participants compared to stroke patients (Figure 6.2A). However, the results were not significantly different between the two groups, $F_{(1,16)} = 0.94$, $p = 0.35$. Differently from absolute errors, no effect of target on signed errors was detected, $F_{(2,32)} = 0.48$, $p = 0.62$. Mean errors for contralateral, central, and ipsilateral targets were 0.9 ± 0.5 cm, 1.3 ± 0.5 cm and 1.4 ± 0.7 cm for the control group, and 0.6 ± 0.6 cm, 0.6 ± 0.5 cm and 0.3 ± 0.7 cm for the stroke group (Figure 6.2B). Also no interaction effect was detected, $F_{(2,32)} = 1.37$, $p = 0.27$.

Comparison of each stroke participant with the average control subject revealed a higher error for subjects S2, S4 and S5, as shown in figure (Figure 6.2C). While subject S2 undershot the target in all the trials, the opposite trend was found for subject S4 which always overshot. The significant differences between control group and stroke participants were found in the contralateral and central targets for patient S2 and in all targets for patient S4, while patient S5 showed a decreased proprioceptive acuity only in the ipsilateral direction (Table 6.3).

Table 6.3: *Pairwise comparisons of Signed errors between each subject and the control group in the 3 directions. Mean differences are evaluated as Control-S. Significant differences are marked with an asterisk.*

S	Contralateral		Central		Ipsilateral	
	Mean Difference	p-value	Mean Difference	p-value	Mean Difference	p-value
1	1.1	0.06	0.8	0.37	2.2	0.01
2	-3.3	<0.005*	-2.8	<0.005*	-2.3	0.01
3	0.8	0.15	1.9	0.03	-0.6	0.48
4	3.5	<0.005*	3.8	<0.005*	5.9	<0.005*
5	0.8	0.15	1.4	0.11	2.6	<0.005*
6	-0.5	0.36	0.3	0.76	-0.9	0.30
7	-0.3	0.64	1.3	0.13	1.8	0.03
8	0.9	0.14	0.6	0.52	0.8	0.31
9	0.7	0.21	0.1	0.94	-0.3	0.72

Variability

Stroke patients showed a more variable estimation of the target position (1.3 ± 0.1 cm) compared to the control group (0.9 ± 0.1 cm), as shown in Figure 6.3A. However, the statistical analysis failed to detect a significant difference in matching precision between groups, $F_{(1,16)} = 3.85$, $p = 0.07$. There was a significant effect of target, $F_{(2,32)} = 4.41$, $p = 0.02$: the lowest variability was found for the contralateral target (control group: 0.8 ± 0.1 cm; stroke group: 1.0 ± 0.2 cm), followed by the central (control group: 0.9 ± 0.2 ; stroke group: 1.5 ± 0.3) and the ipsilateral target (control group: 1.0 ± 0.1 cm; stroke group: 1.5 ± 0.3 cm). Also for this metric, the interaction between Group and Target was not significant, $F_{(2,32)} = 1.62$, $p = 0.21$. While the central target was identified with similar variability as the ipsilateral (mean

Figure 6.3: (A) Box-plot of variability for the two groups. (B) Mean variability in the 3 directions for the two groups, where the gray squares represents data from the control group and black circles represent stroke patients.

difference $\pm$ SEM: 0.0 ± 0.2 cm, $p=1$) and the contralateral (0.3 ± 0.1 cm, $p = 0.74$), the difference between contralateral and ipsilateral matching precision (0.3 ± 0.1 cm) was significant ($p = 0.01$), as revealed by the post-hoc analysis (Figure 6.3B).

6.2 Clinical applicability and validity of the passive JPM task

Stroke results in abnormal muscle coactivation of shoulder abductors and elbow flexors of the paretic arm during reaching movements [251] which are marked for individuals with moderate to severe stroke [252–254]. The abnormal coactivation results in a reduced active range of motion, as extensively documented in the work of Beer et al. [37,253,255] which would affect the matching performance in an active proprioceptive task. The method proposed in this work allows the assessment of joint position sense independently of the severity of motor impairments as the movement is fully assisted by the robotic device. Patients with the lowest FMA score were, in fact, able to accurately identify the target position even in presence of reduced motor functions (See Figure 6.1C and Figure 6.2C). Further, all participants were fully able to understand and complete the proprioceptive assessment, which was inherently simple. Hence the proposed approach can be applied to a large spectrum of population.

Further, due to the modest time required for the proposed assessment (less than

10 min), it can be included in conjunction with conventional motor assessments [256] or robotic assessments, such as the ones proposed by Hussain et al. administrated with the same robotic device [257], or other methods reported in literature [258,259]. As a consequence, regular assessments can be carried out to detect changes in joint position sense over time, unveiling a more detailed insight into the relationship between training and sensorimotor recovery.

While the proposed procedure avoids non-proprioceptive modalities which could be sources of errors, it cannot rule out the possibility that the measured acuity is affected by a memory component. For this reason, clinicians should prefer different tests when assessing individuals with memory issues, such as a matching task in presence of a persistent visual reference position or a contralateral matching task (i.e. opposing limb sets the target configuration throughout the task). This last procedure has, however, the limitation of not being able to ascertain whether the errors are due to noise in the perception of the reference arm position or of the matching arm [94].

The observed low intrasubject variability within control participants is consistent with previous findings [226] on joint position sense of healthy participants in a broader age range presented in Chapter 5, making the proposed technique robust for providing a sensitive measure that allows the detection of proprioceptive deficits. Compared to clinical tests (i.e. RASP [51] and NSA [49]), in which proprioceptive tests simply assess the patients' ability to determine in which direction a joint has been moved or to mirror the change of movement with the unimpaired limb within an error of 10° , the proposed robotic assessment provides a quantitative and automated measure of joint position sense. Moreover, the test is more repetitive, reliable and sensitive, and could eliminate the problem of low inter-rater reliability which affects the conventional scales.

In this study, we compared the matching error and variability of position estimation of the stroke group with data obtained from age-matched healthy participants. Although control participants had a lower absolute error and variability, we did not observe significant differences between the two groups. This finding suggests that the majority of stroke participants were not different from the control group and therefore had intact proprioception. A closer inspection of data of individual participants revealed that two patients had a significantly different matching performance

compared to the mean results of the control group. Namely, subjects S2 and S4 consistently recognized the target position with higher error compared to the mean absolute, and signed errors of the control subjects, while we found a proprioceptive deficit in only one direction for subject S5. This is in accordance with other studies that show that not all patients are affected by proprioceptive deficits: Dukelow et al. found that about 50% of total sub-acute stroke patients examined presented some element of proprioception impairment [82]. In another study, Semrau et al. found that, in a group of 56 patients, there was a trend for the 48% who displayed proprioceptive deficits one week after stroke to relearn proprioceptive skills throughout the course of the first 6 months of recovery [260]. Their finding suggests that a lower percentage of chronic stroke patients are affected by proprioceptive deficits, which is in line with our results.

The two subjects with joint position sense deficits presented a lesion which can generate proprioceptive impairments: S2 had a lacunar stroke with a lesion in the left corona radiata, while S4 had a subcortical stroke involving the right basal ganglia. Corona radiata infarcts have a wide clinical spectrum including incomplete motor and sensory loss [261], and causing sensory disturbances localized to the limbs [262], which also affect proprioception [263]. Basal ganglia are specifically involved in the control of movement amplitude [264], with lesions in this area leading to proprioceptive dysfunction [265, 266].

We also found a trend for stroke patients to identify the target position in a more variable fashion compared to the control group, which is consistent with previous results: Dukelow et al. [82] and Leibowitz et al. [93] found a high variance in repeated trials performance of stroke patients compared to healthy individuals. These studies compared matching performance during a bimanual task, in which the position of the affected hand was matched with the healthy hand. Due to the different methodology, however, a direct comparison of matching errors is not possible: the errors obtained in these studies could arise from both arms, not providing a measure of paretic arm joint position sense, as proprioception of both sides can be affected after unilateral stroke [41, 267] due to disturbances of interhemispheric, transcallosal transfer [268, 269]. However, observed similarities in terms of variability outcomes in the proposed and previous studies serve as a good indicator of the validity of the proposed approach.

Another finding supporting the validity of the discussed methodology is that the target position consistently affected the magnitude of the errors of both groups. Proprioception has been found to be not uniform across the workspace, with greater acuity when estimating hand positions closer to the body due to the larger total changes in joint angle associated with hand movements in this area [235]. Matching errors were smaller for the contralateral target: this concurs with results published in a review by Goble [94] which reported matching errors measured for right-handed healthy subjects when matching targets in the right or left workspace. The study found a better performance when matching positions in the left of the body midline (contralateral), especially in the far-left workspace. Also the study of Haggard et al. revealed a contralateral advantage in matching task for right-handed participants, with smaller matching errors for positions in the extreme-left workspace [236].

As described in the previous chapter, we believe that this is due to the fact that movements towards contralateral and central targets involve more joints compared to movements towards the ipsilateral target [237], resulting in higher activity of muscle spindles. Further, movements toward the contralateral target caused the shoulder to go closer to the limits of its ROM, resulting in more tension, a higher receptors sensitivity and therefore enhanced accuracy [238, 239].

Limitations

A limitation of the current study is the small sample of patients examined. For this reason, no relationship between motor and proprioceptive function can be drawn from our results; it is worth anyway to highlight that the two stroke patients (S2 and S4) that performed more poorly than control subjects have some of the highest FMA scores. The relationship between FMA scores and matching performance with the robotic test will be object of future studies.

Moreover, patients were recruited for a randomized control trial evaluating the feasibility of using a robotic device for motor training. The inclusion criteria limited the spectrum of motor and sensory impairments which are present in the stroke population. Due to the lack of clinical scores on joint position sense in this study, we could not establish the correlation between the robotic assessment and the conventional tests. Furthermore, sensitivity and specificity of the proposed test have yet to be determined with a larger number of patients.

A disadvantage of the current paradigm is the addition of delays imposed by having the experimenter pressing the button after the subject verbally reports the reaching of the target position. These delays might introduce noise and bias in the results, which, however, had a limited overall effect on the evaluated position variability (1.3 cm and 0.9 cm for patients and healthy participants respectively) due to the low velocity of the robot. In fact, the reaction time to auditory cues has been documented to be 140-160 ms [270], which would result in an error of about 0.3 cm in the position estimation. An alternative approach to avoid this error is to let the patient press the button. In this experimental condition, the task would become bi-manual, requiring transcallosal transmission from the primary somatosensory region of the cerebral cortex in the contralateral hemisphere to control the action of the unimpaired limb. The interhemispheric transfer would add an additional cognitive factor which may influence the position matching performance.

A future study will further validate the methodology with a larger cohort of stroke-affected population presenting a larger spectrum of impairments. This study will help in establishing normative values of joint position sense acuity that will allow the identification of proprioceptive deficits. The proposed assessment will help therapists in selecting the most appropriate therapy tailored to the patients' need.

6.3 Wrist proprioception in acute and sub-acute stroke patients

Despite continuous advances in the design of task-specific, repetitive, high-intensity training protocols, stroke remains a leading cause of adult disability. Spontaneous recovery can be usually observed in the first weeks following the stroke. Voluntary movements have been registered after 6 days after stroke [271], and motor functions of the arm have been shown to improve and reach the maximum functionality during the first three weeks in 80% of the patients [272]. However, improvements show a high heterogeneity across patients associated with their demographics, behavioral experience, and genetics [273].

While changes in motor functions have been extensively studied, the natural history and neural correlates of spontaneous recovery in somatosensory functions after

stroke have received less attention [107]. In the study by Winward and colleagues, 18 stroke patients were screened by mean of the Rivermead Assessment of Somatosensory Performance over a 6-month period. While none of the participants had fully preserved sensation in the acute stage of stroke, different degrees of recovery were observed in most of the sensory modalities during the study period, especially in proprioception which showed the most recovery [274]. Similarly, among the 56 patients recruited for the study by Semrau et al., almost half of the patients presenting deficits in proprioception one week after stroke improved during the first 6 months of recovery [260]. This could explain why the proposed protocol was not able to discriminate between the control group and stroke patients (screened between 5 and 24 months after stroke) as patients may have had some recovery of somatosensation following stroke, and a low number of chronic patients presented proprioceptive impairments.

There is indeed evidence of lower proprioceptive performance in sub-acute stroke patients compared to healthy subjects. Kattenstroth et al. analyzed the recovery of joint position sense of the fingers of 10 patients (mean weeks post stroke = 2.3) before and after 2 weeks of hospital-based rehabilitation and found significant improvements in performance, which, however, was still below that of a healthy age-matched control group (10 individuals) [275]. In another study, the assessment of wrist position sense of 51 patients (mean days post-stroke = 49.5), revealed that 49% of the patients showed impairments of the affected wrist, and that also the ipsilesional wrist presented a less severe impairment in the 20% of participants [276]. In this latter study, the protocol chosen to test the wrist matching performance involved the assessment of the error between the wrist angle, passively reached with the help of the experimenter, and a pointer aligned by the patient to the imagined line between the middle of the wrist to the index finger.

As sensory dysfunctions may resolve with time, we tested the validity of the revised JPM protocol on a group of acute and sub-acute patients (0-3 months post stroke) participating to a study designed to determine the incidence of proprioceptive deficits on admission, discharge and follow-up from rehabilitation using standardized clinical tools and robotic scales. The main objectives of the ongoing study is to obtain baseline data to increase the understanding of the incidence, evolution and impact of somatosensory and proprioceptive impairments on post-stroke recovery, as

well as to test the feasibility of using the Wrist device to safely obtain quantitative wrist joint proprioceptive measurements at the three time points within tolerance of stroke subjects.

We hypothesized that, in accordance to the studies previously described, the test is able to discriminate between the control and stroke group, for which proprioception of the wrist is expected to be impaired in a higher percentage of the population analyzed at admission.

6.3.1 Participants and procedure

Nine stroke survivors (7 males, mean age $\pm$ SD: 54 $\pm$ 12.1 years), met the inclusion criteria for participating in the study: (1) first clinical stroke (ischaemic or haemorrhagic) diagnosed by brain imaging CT or MRI; (2) age between 21 years to 85 years; (3) less than 90 days of stroke on admission to rehabilitation; (4) medical and neurological stability; (5) presence of either motor and /or sensory deficit detected by clinical examination; (6) ability to understand simple instructions. Patients were excluded if they presented: concomitant orthopaedic conditions limiting the wrist range of motion (active arm/wrist fractures, fixed contractures, arthritis and/or wrist fusion), arm or wrist joint pain (Visual Analogue scale VAS $>5/10$), wrist spasticity (modified Ashworth Scale score ≥ 2), instability and/or severe hemispatial neglect. All participants were screened by mean of the Montreal Cognitive Assessment (MoCA) [277], which resulted in scores $> 28/30$, indicating the absence of cognitive impairments. Patients' demographic data are reported in Table 6.4. Prior to recruitment, patients signed the informed consent form which conformed to the ethical standards expressed in the 1964 Declaration of Helsinki. The study methodology was approved by the Domain Specific Review Board of the National Healthcare Group (NHG).

Participants sat comfortably on a height-adjustable chair next to the robotic device, placed their forearms on the arm support, holding the handle which was placed in the neutral position set to 0° in all DoFs. The height of the chair and the position of the robot, which was placed on a side table on casters, were adjusted so that the participants' shoulder was abducted at $\sim 30^\circ$, their elbow was flexed at $\sim 90^\circ$, and the arm formed $\sim 30^\circ$ from the frontal plane. After visually inspecting the alignment of the affected wrist joint with the center of motion of the robot

Table 6.4: *Acute and sub-acute stroke patients characteristics.*

Subject ID	Age (years)	Gender	Handedness	Time since onset (days)	Nature (Haemorrhagic or Ischaemic)	Paretic Wrist	FMA (0-66)
S1	56	M	R	11	I	L	50
S2	36	M	R	22	H	L	4
S3	70	M	R	11	I	L	4
S4	57	M	R	38	I	L	12
S5	46	M	R	24	H	R	66
S6	51	M	R	9	I	L	64
S7	59	M	R	44	H	R	26
S8	40	F	R	9	I	L	52
S9	71	F	R	13	I	R	61

and making the necessary adjustments, the participants' forearm was secured to the robot using Velcro strips. Patients were instructed to face forwards, to keep the affected arm and wrist relaxed during the whole duration of the experiment and to hold the stop button with their unaffected hand.

Patients' proprioception was assessed with an ipsilateral JPM procedure, described in Section 5.3.1, for each of the wrists DoFs within the functional ROM. Patients were blindfolded for all the duration of the test. Each trial consisted in three separate phases: 1) from the initial position, the robot passively moved one of the three DoF to a preset constant position or proprioceptive target (Criterion movement), maintained it for 2 seconds 2) and then moves the joint back to the initial configuration; 3) in the third phase the robot passively moved the wrist in the same DoF and the patient was requested to stop the movement by pressing the hand-held button when he felt that the target position was matched (Matching movement). Finally, the robot brought the subject's wrist back again to the initial position for the next trial. Patients did not receive any feedback on their online performance to eliminate the possibility of recalibration of the responses during testing, based on the direct knowledge of performance. Criterion and Matching movements were displayed by the robot, at a respective velocity of $8^\circ/\text{s}$ and $5^\circ/\text{s}$. Targets were set at $\pm 30^\circ$ for FE, $\pm 20^\circ$ for AA and $\pm 30^\circ$ for PS. Patients performed a total of 6 target sets, where a target set consisted in 6 trials with target position in Flexion, Extension, Abduction, Adduction, Pronation, Supination, resulting in a total of 36 trials. After two target sets, a 1-minute break was provided to avoid drift in the proprioceptive sense. The duration of the complete JPM task was ~ 10 minutes.

Figure 6.4: Radar plots of (A) Absolute errors, (B) Signed errors and (C) Variability for the two groups in the different directions. Gray lines refer to the Stroke group, while black lines refer to the Control group.

6.3.2 Data analysis and results

Wrist proprioception was measured in terms of Absolute error, Signed error, and Variability. For each patient, the median value across trials was used as measures of absolute and signed error. Data were checked for normality and sphericity and were compared to the data collected from the control group composed of 12 healthy participants described in Section 5.3.2. Differences in proprioceptive performance were analyzed with a mixed ANOVA with between-factor Group (Stroke, Control) and within-factor Target (Flexion, Extension, Abduction, Adduction, Pronation, Supination). Results with p -values < 0.05 were considered significant and were submitted to Bonferroni corrected post-hoc analyses.

Mean Absolute error $\pm$ SEM evaluated in the Stroke group was $5.6 \pm 0.4^\circ$, which resulted significantly higher compared to that of the control group ($3.7 \pm 0.3^\circ$), $F_{(1,19)} = 14.81$, $p = 0.001$. The analysis revealed also a significant effect of Target, $F_{(5,95)} = 2.38$, $p = 0.04$, and an interaction effect between Group and Target, $F_{(5,95)} = 2.88$, $p = 0.02$. Errors magnitude was higher for the Stroke group in all movement directions, as shown in Figure 6.4A, and the post-hoc analysis detected significant difference between the two groups for movements in Extension (mean difference $\pm$ SEM = $4.08 \pm 1.0^\circ$) and Adduction ($3.17 \pm 0.8^\circ$), both $p = 0.01$.

The analysis of Signed errors showed the tendency to overshoot the target positions for both groups in all movement directions (Figure 6.4B). Matching performed by stroke patients resulted in an average Signed error of $-2.3 \pm 1.2^\circ$ which was similar to the analogous error for the control group ($-1.1 \pm 1.0^\circ$), $F_{(1,19)} = 0.66$, $p = 0.43$.

An effect of Target was found, $F_{(5,95)} = 3.48$, $p = 0.006$, with greater overshooting amplitude in the PS DoF ($< -2.33^\circ$) and no preference in over/undershooting in Abduction ($-0.1 \pm 0.8^\circ$). The post-hoc analysis reported significant differences between Abduction and Adduction (mean difference $\pm$ SEM = $2.2 \pm 0.5^\circ$) and Abduction and Pronation $\pm 0.6^\circ$ ($3.6 \pm 0.8^\circ$). Figure 6.2B). No interaction between Target and Group was found, $F_{(5,95)} = 1.24$, $p = 0.30$.

Stroke patients showed a more variable estimation of the target position ($4.2 \pm 0.6^\circ$) compared to the control group ($2.7 \pm 0.5^\circ$). However, the statistical analysis failed to detect a significant difference in matching precision between groups, $F_{(1,19)} = 3.56$, $p = 0.07$. Variability was similar independently from movement direction, $F_{(5,95)} = 1.71$, $p = 0.14$, and ranged from $2.8 \pm 0.3^\circ$ for Abduction to $4.1 \pm 0.6^\circ$ for Flexion. Variability is shown in Figure 6.4C.

6.4 Validity and sensitivity of passive JPM for wrist proprioceptive assessment in stroke population

The goal of this study was to determine the feasibility of using the passive joint position matching task delivered by a robotic device to detect proprioceptive deficits of the wrist after stroke. Data reported in this section represent the first part of a database which will allow to increase the understanding of the incidence of proprioceptive impairments post-stroke, their consequence on recovery and to support the integration of the diagnostic and therapeutic aspects of robotic interventions.

In this preliminary study, we compared matching errors and variability of position estimation of acute and sub-acute stroke patients with control data to verify the robustness of the proposed approach in differentiating between healthy and stroke participants in relation to movement dependence. We limited the effect of non-sensory factors, including motor impairment, inadequate comprehension and visuo-perceptual impairment by passively imposing wrist positions and by using selection criteria that excluded the presence of cognitive issues and neglect. We also removed the delays imposed by having the experimenter pressing the button, as all patients were able to hold and press the button as requested.

All participants could complete the assessment thanks to the passive nature of the test, for which wrist movements were imposed by the robot, allowing the screening of highly impaired patients, such as S2, S3 and S4 (FMA score of 4, 4 and 12 respectively). The robotic test can be therefore implemented in clinical settings to screen a wide range of stroke patients, at the same time limiting problems of inter-rater variability and can reduce costs by lowering the reliance of a clinician or therapist to obtain proprioceptive diagnostics.

The analysis of matching errors of the stroke group revealed that, similarly to healthy participants, patients systematically overshoot the target position, but that the magnitude of the errors was significantly higher than the control group, and that the final position estimate was, in general, more variable, but not statistically different, than the one observed in the control group. These results support the previous findings reporting the presence of a significant proportion of patients displaying somatosensory impairments after stroke [275,276], while do not corroborate the results obtained by Niessen et al, who did not find differences in performance for passive reproduction of shoulder positions between 22 patients and 10 control subjects [267]. Proprioceptive scores are joint specific and should not be generalized to other body locations due to the high variability in lesion site and severity of stroke. Moreover, in this last study, joint position sense was evaluated 14.7 weeks post-stroke, which was superior to the studies by the groups of Kattenstroth and Carey (2.3 and 7 weeks respectively). In our study, patients were screened before an average of 20 days post-stroke, with 5 patients screened within two weeks from the event. Therefore, it is possible that our results better captures the transient loss or disturbance in sensation occurring during the first weeks post-stroke [30] in comparison to the other studies. A future study will address this point by evaluating proprioceptive changes over time through multiple assessments by mean of the same device in order to evaluate its association with rehabilitation procedures as well as natural recovery.

Our results show an expected anisotropy in matching accuracy, with smaller Absolute errors recorded for the AA DoF, and different preference for target over or undershooting between AA and PS, is in line with the results presented in the previous chapters, and provide evidence in support of the good sensitivity of the protocol for detecting small differences in acuity in the different DoFs. Differences may be

related to the mechanoreceptor density and innervation: as previously reported, in fact, less innervated ligaments are stressed during FE and PS. Moreover, the common trend of target overshooting in PS can be related to the different anatomical districts involved (the proximal radioulnar joint and the distal radioulnar joint) and consequently different sets of muscles, ligaments and hence mechanoreceptors [278].

6.5 Summary

There is a clear distinction between research-oriented measures of proprioception and those used in clinical settings. Technologies employed to obtain the former measures allow for more precise, accurate, and reliable assessments, particularly in terms of limiting the influence of factors other than proprioception in affecting the outcome; however the clinical applicability associated with these measures is usually limited due to the amount of equipment required, technical expertise and time required for their administration. As an example, although the psychometric methods have high sensitivity, they require an extensive amount of time and precise manipulation of limb joints for their implementation, hence limiting their applicability in clinical environments. In contrast, current clinically friendly conventionally used tests have very limited sensitivity due to ordinal nature. In this study, we propose a sensitive measure of joint position sense which can be translated into clinical practice and can be administrated with the same robotic technology designed for motor rehabilitation. Future studies will investigate the applicability of such measure for assessing the effect of rehabilitation programs on proprioception.

Conclusions and future work

Proprioception, our sense of body position, may be severely impaired by neurological conditions such as stroke. Despite its importance for the control of voluntary movements, clinical assessments of proprioception lack reliability and sensitivity.

In this thesis, we evaluated the methodologies, reliability, and feasibility of robotic proprioceptive assessment in healthy individuals and stroke patients. The assessment employed two different robotic devices: a 3-DoF manipulandum designed for the training of the wrist, the Wrist robot, and a planar robot for rehabilitation of the upper limb, the H-Man. Determining the feasibility of using robotic technology to assess an individual's proprioceptive status can provide a precious tool for clinicians to design rehabilitation programs to serve patients after neurological diseases.

This thesis reports evidence for the feasibility of robotic-aided proprioceptive assessment: robotic technology can generate robust, repetitive, reliable and unbiased metrics for the assessment, which are sensitive enough to detect small differences in proprioceptive acuity across wrist DoFs and across arm movements. In consideration that stroke can affect both sides of the body independently from the patients' handedness, proprioception of both dominant and non-dominant wrists and arm was characterized, which resulted similar despite hand dominance. Other factors affecting proprioception have been analyzed: interaction between reafferent and exafferent signals generated during wrist movements, the presence of forces during the matching task and ipsilateral vs contralateral matching. The evaluation of the interaction between reafferent and exafferent signals generated during active movements in the JPM test showed that due to differences in visual and kinesthetic information available, the perception of wrist position is more accurate when participants replicated the target position after it has been passively displayed. External forces do not decrease proprioceptive performance due to the ability of our central nervous system to discriminate joint position sense and sense of force. The comparison between ipsilateral (unimanual) and contralateral (bilateral) test showed that, according to the proprioceptive sensory-motor gain hypothesis, proprioception was more accurate and more consistent when the same side of the body is used to acquire and replicate a target position. The position matching task was modified to account for the practical limitations of the adoption of such test in clinical settings.

In particular, the revised test can be carried out independently from the presence of motor impairment and has a limited duration. The method, inherently simple, was still sensitive enough to discriminate the small differences in matching performance across movement direction of both arm and wrist joint. The method was then applied in clinical settings to detect changes in proprioceptive status of patients in the acute, sub-acute and chronic stages after stroke. The revised proprioceptive assessment can be translated into clinical practice and can be administrated with the same robotic technology designed for motor rehabilitation.

As future work, a direct comparison between the results obtained with the clinical tests and the ones obtained with the robotic tests presented in this thesis should be evaluated. The comparison would increase the understanding of the incidence of proprioceptive impairments post-stroke and would support the integration of the diagnostic and therapeutic aspects of robotic interventions. It would also determine the advantages for clinicians to transit from the clinical tests to the methodologies presented in this thesis. The practical advantages mentioned in this thesis consist in the simplicity of the test so that all patients could understand and perform the task. Moreover, the limited time required to test the patients allows the inclusion of such tests in conjunction with motor assessments, which can be administered with conventional scales or with the same robotic devices employed for the proprioceptive assessment. Thus, robotic technology can help in reducing the costs associated with the amount of individual attention from clinicians and therapists and the costs associated with the diagnostic tools. In future studies, the comparison between clinical and robotic assessment can also address the advantages and limitation of the robotic procedure in terms of time to set up patients, discomfort, fatigue and cognitive load. Automated methods to determine the presence of impairments could also be established to facilitate the adoption by clinicians of the techniques tested in this thesis.

A limitation of the studies presented is that no electromyographic (EMG) was measured from the muscles involved in wrist and arm movements during the tests. Therefore, it cannot be excluded that subjects might have not been completely relaxed during the passive motion, or that they could have resisted such movement, possibly affecting the results and making the task more difficult for patients. This problem can be caused by the lack of familiarity with the device, which can affect the

early stages of the experiments. To address this issue, participants performed a series of familiarization trials in which they were instructed to avoid co-contraction of the arm muscles. Future studies can explore new methodologies to ensure participant's relaxation during the whole assessment, which can involve the analysis of the torque profiles generated by the robotic devices or by measuring EMG activity during the task. In the latter case, particular attention must be paid to electrodes placement to ensure participant's comfort, considering that for the wrist assessment, the forearm is strapped to the rigid cast. Moreover, the placement of EMG electrodes could increase the time necessary for the patients set up, and practical advantages in using this approach compared to the use of sensors or torque readings from the motors have to be evaluated.

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