



Università Campus Bio-Medico di Roma

Corso di dottorato di ricerca in
SCIENZE BIOMEDICHE INTEGRATE E BIOETICA
XXXV ciclo a.a. 2019-2020

**Body Representation:
Insights from Health to Pathological Models**

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06/12/2023

Abstract

Body representation is a dynamic concept and refers both to stable and adaptable components of how the brain integrates multisensory information relative to body (such as position, posture, shape etc.) and related cognitive and affective processes (body knowledge, beliefs, feelings etc.). Here I explore various aspects of body representation in healthy and pathological models, including its neural basis, plasticity, and its role in conditions like phantom limb pain (PLP).

Firstly, focusing on the hand, my colleagues and I confirm the hypothesis of the presence of a standard postural representation of the hand, and disclose its neural origin. This study unveils the existence of a predetermined and stable component within body representation. Understanding the neural circuits governing this standard posture could open new avenues for therapeutic interventions, particularly in prosthetic and rehabilitative contexts. Furthermore, we explore the malleability of body representation using virtual reality, demonstrating that immersivity can impact the perceived dimensions of one's body, in variable extents when comparing exteroceptive and proprioceptive reported measures of the forearm.

To clarify clinical impacts of altered body representations, my colleagues and I studied PLP, which is considered a very common sequela after amputation. By analysing various physiological models, we uncover the multifaceted nature of the disorder. Among its possible causes, a disrupted body representation due to the lack of feedback coming from the lost limb area luckily plays a pivotal role. Moreover, our analysis suggests that effective treatments for PLP may require a comprehensive approach, tailored to individual needs.

To delve deeper into the impact of body representation on pain, my colleagues and I tested healthy participants in virtual environment, by comparing the impact of different appearances of the upper limb (e.g., hand visibility, arm length and presence of the injury) on the pain perception and autonomic responses. The lack of hand visibility resulted in exacerbation of perceived pain and decrease in autonomic response showing a central role of the missing pain source. The arm length and the presence of the injury also have an impact on autonomic response. We disclosed an intricate relationship between visual feedback alteration, body image-related unpleasantness, and virtual reality immersion quality.

Finally, my colleagues and I analysed several methods to incorporate non-invasive proprioceptive feedback strategies in the recovery of altered body representation. While no one-size-fits-all approach is identified, we delineate the advantages and disadvantages of the discussed methods, offering guidance for future interventions.

Overall, this PhD project thesis aims to underline the utility of VR in understanding body representation and pain and its possible application in alleviating PLP in people who have undergone amputations. Moreover, in a vision of a fully restored body representation it would suggest that feedback restitution, specifically visual and proprioceptive ones, is essential to recovery the bodily integrity.

Author's publications

Di Pino, G., **Piombino, V.**, Carassiti, M., Ortiz-Catalan, M. Neurophysiological models of phantom limb pain: what can be learnt. *Minerva Anestesiologica* (2021) Apr; 87(4):481-487. doi: 10.23736/S0375-9393.20.15067-3. Epub 2021 Jan 12. PMID: 33432796

Papaleo, E.D., D'Alonzo, M., Fiori, F., **Piombino, V.** *et al.* Integration of proprioception in upper limb prostheses through non-invasive strategies: a review. *J NeuroEngineering Rehabil* 20, 118 (2023). <https://doi.org/10.1186/s12984-023-01242-4>

Le Jeune F., D'Alonzo M., **Piombino V.**, Noccaro A., Formica D., Di Pino G. Experiencing an elongated limb in virtual reality modifies the tactile distance perception of the corresponding real limb (under review).

Piombino V., D'Alonzo M., Castro F., Di Lazzaro V., Di Pino G. Cerebral circuits involved in preferential hand posture representation for action (in preparation).

Piombino, V., Maciejewska, K., D'Alonzo, M., Papaleo, E.D., Di Pino, G. Vision feedback in modulation of pain perception: neurophysiological perspective on a virtual reality Phantom Limb Pain modelling (2023). Poster presented at the 13th congress of European Pain Federation (EFIC 2023), Budapest.

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1 Introduction

1.1 Motivation and Objective

Laboratory experimentation allows us to artificially recreate natural phenomena and dissect them into their constituent parts for study. Understanding how the brain represents the body provides us with a privileged point of view from which we can chart new paths to address medical issues that afflict specific populations, in our case amputees. Throughout this investigation, I have had the opportunity to explore the body representation, both in its innate and adaptable aspects, and explore the contributions of sensory modalities to its construction. Vision plays a prominent role, often exerting dominance over other sensory modalities in shaping our representations of the body. Additionally, touch and proprioception play integral roles in this intricate orchestration of sensory inputs.

I have delved into the complexities of amputation, neuroplasticity, and phantom limb pain. This exploration has unveiled the challenges faced by individuals who have undergone limb loss, shedding light on the interplay between the brain's representation of the body and the perception of pain in the absence of a physical limb. Through this work, it has become clear that comprehending and recovering body representation is not just a scientific pursuit but a means to enhance the quality of life for those who have experienced amputations. The concept of embodiment assumes a pivotal role, bridging the gap between amputees and their artificial limbs. It encompasses the experience of ownership and agency over a corporeal entity, offering hope for reestablishing the connection between the individual and their (prosthetic) limb.

These paragraphs provide an overview of body representation, starting from its fundamental mechanisms and leading to its involvement in understanding the clinical phenomenon of phantom limb pain, as well as in planning interventions to restore sensory feedback through prosthetics.

1.2 Thesis Outline

Chapter 2 introduces the reader to the concept of body representation. Alongside this, it explores phantom limb pain as a common consequence of altered body representation and, by considering the embodiment perspective, the notion that this condition could potentially be alleviated through the restoration of missing feedback in amputees. In this view, embodiment of a prosthesis could help reconcile the incongruences in the body representation.

Chapter 3 is based on a paper in preparation and examines the hand representation in the brain of healthy subjects. Here, starting from previous findings which show a postural advantage for action, we investigated cortical circuits involved in the so called “standard posture” of the hand. In identifying the cerebral circuits responsible for the facilitation of action computation and providing insights on the standard posture, we highlight the stable component of body representation as evolution’s heritage and its potential application in brain stimulation protocols.

Chapter 4 is based on a paper under revision. Alongside the idea of prototypical body representation of chapter 3, here, instead, it emerges how the body representation can be updated based on sensory feedback, leading to changes in the perception of one's own body. In this example of perceptual changes through the manipulation of body representation with virtual reality (VR), the observed perceptual changes predominantly emerged from the VR immersion itself rather than through visuo-tactile stimulation. This highlights the crucial influence of visual feedback in shaping body representation.

Chapter 5 provides a clear example of how the normal body representation is altered, as in the case of individuals who have undergone a limb amputation. This chapter from a published critical review of the literature (DOI: [10.23736/S0375-9393.20.15067-3](https://doi.org/10.23736/S0375-9393.20.15067-3)) explores the neurophysiological causes of phantom limb pain and proposes a multifactorial model to interpret and, therefore, treat the phenomenon.

Chapter 6, following the critical analysis in chapter 5, focuses on the mismatch between sensory inputs (i.e., vision and proprioception) in generating phantom limb pain. The aim of this chapter, based on ongoing research work (here preliminary data are discussed), is to provide a VR modelling of the disorder by giving to the virtual environment user the experience of having several altered body images. How previously showed in literature, altering the visual feedback can modulate pain responses.

Chapter 7, from a published critical review (DOI: [10.1186/s12984-023-01242-4](https://doi.org/10.1186/s12984-023-01242-4)) in the context of restoring bodily representation by prosthetics, explores the sense of proprioception and discuss several non-invasive approaches for its restoration in amputees. Here, results with different stimulation methods are summarised and compared considering pros and cons of homomodal and heteromodal restitution, encoded information and sensory channel used. This chapter provides a comprehensive overview of the complexities of proprioception restitution and, in the end, advocates

its role in enhancing the embodiment of prosthetic devices and promoting the recovery from phantom limb pain.

Chapter 8 finally sums up the primary achievements of the current thesis and its principal findings. Moreover, it establishes the groundwork for future investigations.

2 Body representation and its alterations

2.1 Body representations

To perceive, understand and interact with the environment we rely on representations of the body which allow the awareness of body shape and posture, the external stimuli localisation and the knowledge of body parts features.

Body representations are based on the integration of sensory information from multiple modalities, including visual, proprioceptive, tactile, and vestibular inputs (Azañón et al., 2016; Medina & Coslett, 2016). Despite this constant flow of information updates the brain representation in a short-term on-line view, the brain harmoniously fuses these sensory signals even to generate coherent and stable long-term representations (de Vignemont, 2010; Merleau-Ponty, 1945).

Body representation is a profoundly multifaced construct that encompasses various dimensions of human self-perception. To date, confirming the huge variability of its definition, many taxonomic models have been formulated. On one hand, dyadic models focus on the typology of sensory information (exteroception vs proprioception) (Paillard, 1999), level of consciousness (nonconscious vs conscious) (Gallagher, 2005) or source of knowledge (experiential vs semantic) (Longo, Azañón, & Haggard, 2010). On the other hand, multi-representational models, based on nervous system disorders, propose the concurrent presence of more specific modules designated for distinct information (Schwoebel & Coslett, 2005; Sirigu, Grafman, Bressler, & Sunderland, 1991). Indeed, body representations are not necessary mutually exclusive and they can be arranged in a specialised and hierarchical manner (Bratch, Chen, Engel, & Kersten, 2021) acting at different levels and co-participating to the perception of bodily integrity.

Despite this layered view of body representation, we consider two main concepts to hold particular significance in this context: the body schema and the body image. The body schema refers to an internal representation of the body's structure, organisation, and spatial relationships, created through sensory-motor experiences to guide actions (de Vignemont, 2010; Dijkerman & de Haan, 2007). The brain continually process incoming sensory information from skin receptors and proprioceptors (Proske & Gandevia, 2009) and integrates it with motor commands to maintain a seamless coordination of movements. These mechanisms typically operate below the level of conscious awareness, thus the body schema is considered not conscious (Gallagher, 2005). On the other hand, body image is a conscious and cognitive appraisal that can be influenced by societal norms, cultural

factors, and personal experiences. It represents semantic and lexical information about the human body and functions of the body parts (Schwoebel & Coslett, 2005).

2.2 Sensory contribution to body representation

How we portray our body is strongly dependent on the flow of information coming from different sensory modalities and their integration. An extensively studied illustration of such interaction is the *Rubber Hand Illusion* (RHI) (Botvinick & Cohen, 1998), an experimental paradigm by which subjects observe a rubber hand being stroked simultaneously with their hidden real hand being touched. After few seconds of synchronised stimulation, participants often experience a shift in perceived location of their actual hand which seems to be closer to the rubber hand (proprioceptive drift). This illusion is an example of plasticity of body representation. Here, bottom-up and top-down processes interplay in self-attribution: on one hand visuotactile congruency drives the illusion, on the other conceptual interpretation of sensory information provide a meaningful context to the overall experience, contributing to the subject's perception of the rubber hand as a part of their own body representation (Tsakiris & Haggard, 2005).

Considering the complex interaction between multiple sensory inputs in shaping body representations, disentangling the individual contribution of each sensory modality in forming a cohesive sense of self is challenging. Certainly, vision plays a significant role in modulating body representation through its influence on the perceptual and cognitive processes involved in self-awareness. A clear example of its relevance is the *visual capture*, a phenomenon in which visual information dominates or influences perception over other sensory modalities. For instance, discrimination of touch location may be impaired when a visual distractor is incongruently presented with the tactile target (Pavani, Spence, & Driver, 2000). Thus, the visual system provides crucial information in constructing a coherent and dynamic representation of the body. When visual perception of body parts undergoes changes or disruptions, such as modifications in size (Mancini, Longo, Kammers, & Haggard, 2011) or transparency (Martini, Kiltner, Maselli, & Sanchez-Vives, 2015) it can elicit alterations in several body related functions as pain sensitivity and body ownership. Besides such pivotal role of vision, other modalities such as touch and proprioception, co-participate to this multisensory integration to that observed within an orchestra, where each component functions to achieve a unified and synchronised outcome. Hence, similarly to the vision, proprioception (which will be explored in more detail in chapter 7) may modulate body representation. This is the case of the *tendon vibration illusion* (TVI) which, applying vibration at a certain frequency on the tendon of the biceps or the triceps muscle, induces subjects to experience illusory arm movements (Goodwin,

McCloskey, & Matthews, 1972). During TVI, grasping the nose can induce an illusion wherein the nose is perceived as elongated by up to 30 cm, another compelling observation of body schema plasticity known as *Pinocchio's illusion* (Lackner, 1988).

2.3 Amputation, plasticity, and phantom limb pain

Besides manipulation of body representation through illusions in healthy individuals, alterations are often observed in various medical conditions. Considering the multitude of body representation, a huge variety of pathological manifestations can take place. Neurological patients can perceive the absence of a body part or misattribute it as in *somatoparaphrenia* (Gerstmann, 1942) or, in contrast, the overestimation of a body part size as in *macrosomatoagnosia* (Frederiks, 1963). Despite a preserved comprehension for all other word categories, some patients can show category-specific comprehension deficits restricted to body parts (Suzuki, Yamadori, & Fuji, 1997). Others are unable to localise body parts but retain the ability to name them, a disorder known as *autotopoagnosia* (Guariglia, Piccardi, Puglisi Allegra, & Trallesi, 2002).

Occasionally, the brain is unable to update body representation changes. This is true for anosognosia for hemiplegia and for phantom limb pain. In the first case, due to a lack of awareness of the deficit subjects behave as if they do not have any motor disabilities (Coslett, 2005; Vallar, Bottini, & Sterzi, 2003); in the second one, the brain continues to perceive sensations from a limb that is no longer there (Flor et al., 1995; Makin & Flor, 2020; Ramachandran & Rogers-Ramachandran, 2000) resulting in a mismatch between the actual body and the perceived body. This discrepancy can lead to the perception of pain, discomfort, or other sensations in the phantom limb.

Amputations usually occur after diabetes mellitus, trauma and cancer (Ziegler-Graham, MacKenzie, Ephraim, Travison, & Brookmeyer, 2008). War-related limb loss is also frequent, especially among military members. In religious contexts, amputations are also common as a punishment for crime (Tochukwu Nze Ugorji et al., 2019). Moreover, despite its controversy, amputation is a form of treatment for patients with intractable complex regional pain syndrome (Midbari et al., 2015).

Phantom limb sensations, phantom limb pain and stump pain are extremely common in the amputee population. Due to the overlapping boundaries of these concepts, it is not rare to find any of them mistakenly referred to as one of the others. Nonetheless, scientists agree on defining phantom sensation as the nonpainful feeling that the limb is still present, whereas the phantom limb pain and the stump pain refer to the painful sensation perceived in the lost limb region and the pain arising from the residual stump, respectively. The brain's attempt to reconcile the loss of sensory input and

adjust the body schema to the new reality is a complex neuroplastic process that involves multiple brain regions, and which can, in some cases, fail resulting in such body representation disorders.

These phenomena have intrigued scientists for centuries. It is common knowledge that the first detailed scientific report about the phantom limb pain dates back to 1872, when the American neurologist Silas Weir Mitchell published his work “Injuries of the Nerves and Their Consequences” (Nathanson, 1988). However, he was not the first to describe phantom limbs; before him Ambroise Paré, René Descartes, Aaron Lemon and Charles Bell tried, in different ways, to explain and to deal with these illusory sensations (Finger & Hustwit, 2003).

Up to now, several theories have been formulated to explain the phenomenon, each focusing on different characteristics of the disorder and isolating various causes. Given the complexity of the phenomenon, it is currently believed to be the result of the co-occurrence of different pathological factors as showed in chapter 6.

2.4 Embodiment and restoration of body representation

Understanding the multicomponent nature of phantom limb pain and the layered structure of body representation allows us to manage the consequences of limb loss and design interventions aimed at restoring full functionality to the amputee. In this context, the concept of embodiment takes shape to enable a more intuitive connection between the amputee and their artificial limb.

Embodiment refers to the experience of ownership, agency and self-location over a corporeal entity (Kilteni, Groten, & Slater, 2012a). In other words, the sensation of being inside of a physical body, possessing and controlling its parts. Embodiment is strictly related to the body schema concept: due to its plastic nature, the body schema can integrate spatial and dynamic properties of an external object (Maravita & Iriki, 2004; Yamamoto & Kitazawa, 2001). By combining sensory information from both the body and the tool, the so-called “multisensory integration” (Holmes & Spence, 2005; Stein & Stanford, 2008) guides the construction of a unified and integrated representation of the extended body schema. As with the aforementioned RHI paradigm, such multisensory incorporation results in optimal detection, localisation, and identification of bodily events and properties (de Vignemont, Pitron, & Alsmith, 2021).

Another neurophysiological mechanism that enables embodiment is the *sensorimotor plasticity*, the brain’s ability to adapt and reorganise its network in response to changes in sensory inputs, motor demands or neurological conditions. It can occur at various levels of the nervous system, from the cerebral to the subcortical structures and it involves modifications in neural connections and new synapsis formation (Jones, 2000; Sanes & Donoghue, 2000).

Following de-afferentation and de-efferentation (i.e., after a limb amputation) the “orphan” areas of the cortex and some subcortical structures become responsive to inputs coming from parts of the body adjacent to the lost limb (Di Pino, Guglielmelli, & Rossini, 2009). How does the embodiment of a prosthesis impact brain plasticity? Prosthetic limbs can recruit brain resources normally devoted for hand representation, especially in everyday users. Prosthesis usage seems to shape brain reorganisation, increasing the connectivity between visual and sensorimotor hand-selective areas (van den Heiligenberg et al., 2018). This impact is evident not only in its neurophysiological component but also in the cognitive one. Indeed, an extension of the peripersonal space is observed after training in the use of a prosthesis equipped with an intraneural implant (Di Pino et al., 2020a).

In this perspective, plasticity, multisensory integration, and embodiment constitute essential components of the puzzle that ultimately yields the recovery of body representation by restoring its sensorimotor, perceptual, and social components and, in turn, improving the subject’s quality of life.

3 Cerebral Circuits Involved in Preferential Hand Posture Representation for Action

3.1 Introduction

Perception of our body results from a complex multisensory and sensorimotor integration. A continuous information flow coming from vision, touch, proprioception and other senses is required to build a reliable representation of the body (Maravita, Spence, & Driver, 2003). Although the nature and properties of body representation are still not completely understood, evidence supports the coexistence of its multiple variants (de Vignemont, 2010), which have been suggested to be computationally hierarchical (Limanowski & Friston, 2020; Sirigu et al., 1991). One of them is the body schema, which is the collection of physical features and properties (lengths and forces) needed to obtain a specific configuration of the body in the space (Dijkerman & de Haan, 2007).

Among all possible configuration that a body can have, some specific postures are thought to play a pivotal role in human evolution because of their importance in our interaction with the environment. A seminal study (Bromage & Melzack, 1974a) described subjects that, after a deafferentation by brachial plexus or subarachnoid anaesthesia, report perceiving their body in a stereotyped posture, which was independent of the actual position of the body during the anaesthesia induction. These results lead to the hypothesis of the existence of a predetermined ‘canonical’ body posture which have a key functional impact on sensorimotor functions. Recent studies on hand postures showed that when the hand is configured with the index up and the thumb down, tactile stimuli are detected more efficiently (Figure 1) (Romano, Marini, & Maravita, 2017). Moreover, these spatial associations are not limited to the index finger: further investigations show that somatosensory performance of all fingers, are enhanced when they are in a higher position relative to the thumb (Romano et al., 2019). Thus, the term “preferential” or “standard” has been suggested for the fingers up/thumb down hand posture, which is supposed to be the configuration in which our hand is *a priori* represented in the brain. Slower and less accurate responses (reaction times) observed for the reversed digits position may be due to a discrepancy between the actual position sampled by proprioceptive and visual feedback, and the standard representation of the hand. We previously suggested that the standard thumb down/index up representation has an evolutive genesis, recalling the arboreal locomotion of primates (Romano et al., 2021). This in line with the hypothesis that body information processing mainly evolved to be used for action (de Vignemont, 2010). In a previous study, we showed that planning hand movements is facilitated in the standard configuration, in terms of both cortical

excitability and reaction time, when a pinch grip is performed, as well as only observed, imagined or prepared (Romano et al., 2021).

Although it is known that the frontoparietal network plays a crucial role in multisensory integration and in the formation of the body representations for action (de Vignemont, 2010; Morasso, Casadio, Mohan, Rea, & Zenzeri, 2015), the specific cortical circuits involved in the computation determining the advantage remain unclear. Transcranial Magnetic Stimulation (TMS) tests corticospinal excitability (Di Lazzaro et al., 2004; Pellegrino et al., 2022; Rossini et al., 2015), and can be used in humans to investigate cortical circuits non-invasively. Indeed, different coil orientations have been shown to activate different subsets of neurons, depending on the direction of the current induced in the brain by the coil orientation (Amassian, Quirk, & Stewart, 1990; Di Lazzaro et al., 1998b; Di Lazzaro et al., 2001). Typically, current induced by TMS flows parallel to the surface with little radial component, meaning that TMS produces higher directional current, compared, for instance, to transcranial electrical stimulation (TES) that spreads in all directions (Di Lazzaro & Rothwell, 2014). In epidural recordings, the evoked responses of the motor cortex TMS, i.e. the corticospinal volleys, are termed D-(direct) and I-(indirect) waves according to their latency (Amassian et al., 1990; Day et al., 1989). TES over the hand area mainly evokes a D-wave, supposed to be due to stimulation of corticospinal fibres in the subcortical white matter. On the contrary, TMS produces primarily I-waves activating corticospinal neurons trans-synaptically (Di Lazzaro et al., 1998a; Kaneko, Kawai, Fuchigami, Morita, & Ofuji, 1996; Nakamura, Kitagawa, Kawaguchi, & Tsuji, 1996), namely activating layer 2 and 3, which in turn activate the pyramidal neurons. D- and I-waves recruitment is modulated by the direction of the induced current, which is determined by the coil orientation (Di Lazzaro & Rothwell, 2014). Indeed, D-waves are evoked by TMS only when the stimulation is at high intensity or by the latero-medial (LM) coil orientation, which similarly to TES, activates directly the pyramidal tract (Di Lazzaro et al., 1998a).

TMS is mostly employed in the coil configuration that induce an electric current flowing through the brain with a postero-anterior (PA) direction. By reversing the flow of the current to antero-posterior (AP) direction, the threshold for stimulation increases and the onset of motor evoked potentials (MEPs) is delayed (Di Lazzaro & Rothwell, 2014). The descending volleys evoked by AP orientation can be recruited in the opposite order of PA; sometimes, later I-waves are recruited at lower intensities than the first I-wave (I1). This suggests that the different cortical generators of I1, I2 and I3-waves are differentially sensitive to the direction of the current (Di Lazzaro et al., 2001). Of note, the activity generated by AP direction TMS has been proposed to be produced by cortico-cortical fibres originating from the premotor cortex (PM) and projecting towards the motor cortex (M1) (Di Lazzaro & Ziemann, 2014). In other words, different coil orientations test different patterns of pyramidal tract

activation: PA activation is primarily trans-synaptically, LM directly activates the pyramidal tract, and AP produces a larger activation circuit comprising motor areas beyond M1 (Figure 2). Considering that different coil orientations preferentially activate distinct cerebral circuits and cortico-spinal excitability increases in the standard posture (Romano et al., 2021), the main hypothesis of this work is that the enhanced excitability of the standard posture would be maximised by coil orientation which preferentially activates the intracortical circuit responsible of its advantage. Moreover, it is not known whether inhibitory and/or facilitatory mechanisms responsible for this modulation in different postures mainly occur within M1 or may involve other areas; in the former case such modulation can be revealed by short interval intracortical inhibition (SICI) and intracortical facilitation (ICF). These are paired-pulse TMS paradigms in which a subthreshold conditioning stimulus can suppress or increase the response to a later suprathreshold test stimulus with an interstimulus interval (ISI) of 1-6 ms and 10-25 ms, respectively (Di Lazzaro, Ziemann, & Lemon, 2008; Kujirai et al., 1993a). Both phenomena have a cortical origin because they do not affect spinal excitability (Ziemann, Rothwell, & Ridding, 1996). GABAergic system seems to be implicated in SICI, while glutamatergic system in ICF (Kujirai et al., 1993a). Thus, in parallel to our main objective, our second aim is to assess whether dual-pulses TMS protocols (Kujirai et al., 1993a) can bring out M1 inhibition or excitation phenomena in modulating the postural advantage (Kujirai et al., 1993b).

3.2 Materials and methods

Participants

Twenty-one right-handed participants (9 male, 12 females; mean age: 24.29; SD: 5.25) were enrolled in the study. The sample size has been based on our previous study on the topic (Romano et al., 2021), considering a paired t-test, achieving an effect size of 0.6 and a power superior to 0.8. The study was approved by the local Ethics Committee (EMBODY protocol). All participants signed a written informed consent made in accordance with the Declaration of Helsinki and later amendments.

Experimental protocol

Participants were seated on a comfortable chair with both forearms laying on the armrest. MEPs were collected while participants held their right hand in a c-shape posture, with the thumb opposite to the index finger, as for preparing a pinch grip. In separate blocks, we tested the TMS-evoked corticospinal excitability in three pinch conditions corresponding to different angles of the wrist pronosupination (Figure 1). In one condition, the forearm was rotated so that the thumb was held in

a lower position and the index finger occupied the upper space (i.e., standard posture, Figure 1a). In another condition the hand was upturned, with the index finger in a lower position and the thumb in the upper one (inverse posture, Figure 1b), and in the further condition the hand was held in an intermediate position, with the thumb and the index finger at the same height (thumb-medially fingers-laterally, intermediate posture, Figure 1c).

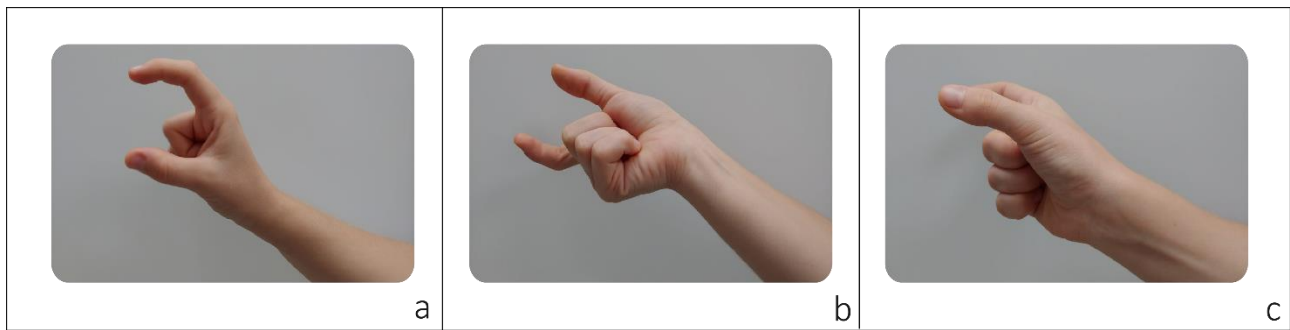


Figure 1, The three c-shape posture configurations. a) Standard posture, b) Inverse posture, c) Intermediate posture.

Coil orientation

The corticospinal excitability in each right-hand posture was investigated in the left hemisphere with three different orientations of the TMS coil: the postero-anterior (PA) orientation with a 45° angle between the handle (looking backwards) and the midline; the latero-medial (LM) orientation (rotated 45° clockwise from PA); and the antero-posterior (AP) (rotated 180° from PA) (Figure 2). Twenty MEPs have been collected for each coil orientation in each posture, for a total of 180 MEPs acquired in each subject. For each posture and coil orientation, MEPs were acquired in a single block, while the factors hand posture and coil orientation were fully randomised.

MEPs were collected by measuring the electromyographic (EMG) response to a single TMS pulse delivered to the M1 cortex by a BiStim² stimulator connected to a D70 (70mm) figure-of-eight coil (The Magstim Co. Ltd). EMG activity was recorded with Ag/AgCl ring electrodes placed on the muscle belly of the *First Dorsal Interosseous* (FDI) muscle of the right hand. This muscle is involved in the index-thumb pinch grip.

For each of the three coil orientations (PA, LM, AP), the hotspot and the resting motor thresholds (rMT) were identified. rMT was determined by gradually increasing stimulation intensity until it evokes MEPs with peak-to-peak amplitude >50 μ V in at least 5 out of 10 pulses (Rossini et al., 2015) in FDI muscle while participants kept their right hand at rest. rMTs was different depending on coil orientation (mean \pm SD PA = 46.30 \pm 10.34%, mean \pm SD LM = 42.50 \pm 8.03%, mean \pm SD AP = 51.00 \pm 12.01% of maximal stimulator output – MSO). MEPs were collected by stimulating the hotspot specific for each coil orientation at 120% of each rMT.

Dual-pulses protocols (SICI and ICF) were run in each of the three postures (standard, inverse, intermediate) employing only PA orientation.

The intensity of the subthreshold conditioning stimulus was set to 80% rMT, while the test stimulus to 120% rMT. Blocks made by twenty trials were collected for each posture in across-subjects randomised order. 3 ms interstimulus interval was used for SICI and 15 ms interval for ICF.

The experimental session lasted on average about 2 hours and 30 minutes.

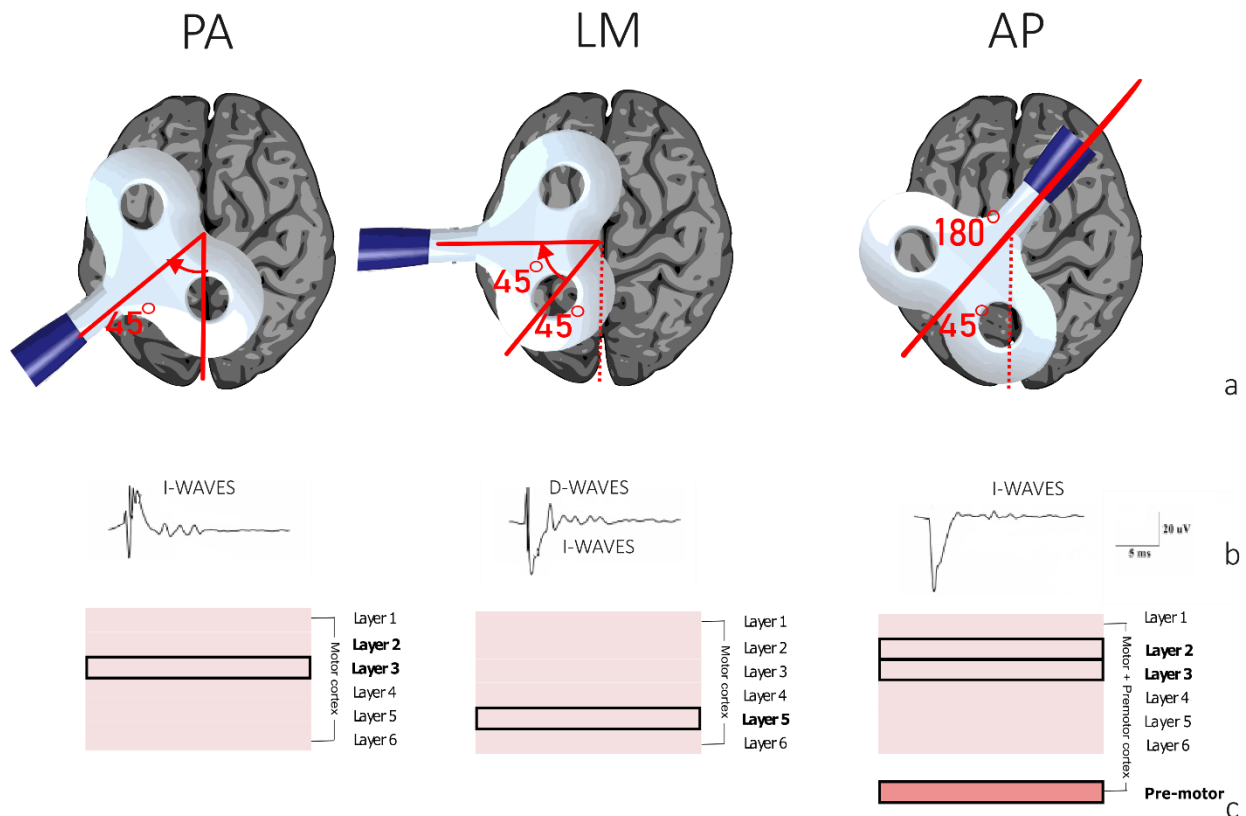


Figure 2, Coil orientations and their relative circuits activations. a) Three different coil positioning with indications in degrees of orientation. b) Descending volleys evoked by different coil orientations registered by epidural electrodes. c) Motor cortex layers and other sites preferentially activated by different coil orientations (Di Lazzaro & Ziemann, 2014).

3.3 Analysis

To process EMG signal, a D360 amplifier (Digitimer, Hertfordshire, UK), a Power1401 A/D converter, and Signal 5.08 software (Cambridge Electronic Design Limited, Cambridge, UK) were employed. The signal was filtered with a 3 to 3000Hz band-pass filter and amplified by a value of 1000.

MEP amplitude was calculated by visually inspecting the EMG responses evoked by the TMS pulse and measuring their peak-to-peak amplitude. For each subject, responses falling beyond the mean \pm 3 standard deviations (SD) were considered outliers and discharged from further analysis (Romano et al., 2021). The EMG root mean square (RMS) in the 1800 to 50 ms time window before the magnetic pulse was taken as measure of pre-TMS muscle tonic activation in the different postures.

To control the effect of the pre-stimulus tonic muscle activity on posture excitability, we compared across postures the EMG activity both in basal condition (RMS) and in the one induced by TMS (MEP). To further reduce the effect of biomechanical factors as muscle activation patterns or force distribution on EMG activity, both MEPs and RMSs responses of the posture of interest (standard, *std*; or inverse, *inv*) were normalised by calculating the relative change (nMEP, nRMS) compared to the intermediate posture (*int*). In other words, the difference between the EMG amplitude in that posture and the one in the intermediate posture divided by the intermediate posture amplitude ($MEP_{std-int/int}$, $RMS_{std-int/int}$, $MEP_{inv-int/int}$, $RMS_{inv-int/int}$) was employed for further analysis. The intermediate posture was selected as normalisation reference because, according to the theory suggesting that the spatial location (up or down) of thumb and index finger impacts on sensorimotor performance (Romano et al., 2017; Romano et al., 2021), such posture is neutral. Positive normalised values indicate an increase of EMG activity compared to the intermediate posture.

Inferential statistics was performed with the statistical software Jasp (0.16.1.0).

Considering the non-normal distribution of data (Shapiro-Wilks test), normalised EMG (both nMEPs and nRMSs) responses were analysed as dependent variables with a Friedman test, a “rmAnova-like” test with the factor “*Condition*” (12 levels generated by the combination of two postures: *std*, *inv*, three coil orientations: PA, LM, AP, and two EMG data type: nMEP, nRMS).

Since we were specifically interested in the postural advantage within the same excited cortical circuit (i.e., tested by a given coil orientation), we run only six pre-planned post-hoc comparisons with Wilcoxon signed-rank test (Bonferroni correction) to compare both the basal and evoked EMG in the two postures: $nMEP_{std}$ vs $nMEP_{inv}$ in PA orientation, $nMEP_{std}$ vs $nMEP_{inv}$ in LM, $nMEP_{std}$ vs $nMEP_{inv}$ in AP orientation, $nRMS_{std}$ vs $nRMS_{inv}$ in PA orientation, $nRMS_{std}$ vs $nRMS_{inv}$ in LM orientation, $nRMS_{std}$ vs $nRMS_{inv}$ in AP orientation.

To test the effect of inhibition and facilitation (SICI and ICF), a paired samples t-test was carried out between test MEPs and conditioned (inhibited or facilitated) MEPs for each posture (standard, inverse and intermediate).

Percentage increases or decreases of MEPs in SICI and ICF protocols were calculated by subtracting the response of the test stimulus from the one of the conditioned stimuli and then dividing the result for the response of the test stimulus ($100 * (\text{conditioned stimulus response} - \text{test stimulus response}) / \text{test stimulus response}$) for all the postures. Data were not normally distributed (Shapiro-Wilk test). Then, the conditioned percentage of the intermediate posture was subtracted from the one of the standard posture and inverse posture (nSICI, nICF) to obtain a “delta value” (%inhibition_{std-int}, %inhibition_{inv-int}, %excitation_{std-int}, %excitation_{inv-int}). Since, unlike MEPs and RMSs, SICI and ICF values already resulted from a normalisation, to preserve the direction of changes and the consistency of data, it was considered appropriate to prefer a delta approach than a further relative increase.

To compare nSICI and nICF between postures, two separated analyses were performed.

A t-test was run to compare nICF_{std} with nICF_{inv}, whereas a Wilcoxon signed-rank was performed to compare nSICI_{std} with nSICI_{inv} because nSICI data were not normally distributed (Shapiro-Wilk test).

3.4 Results

The Friedman ANOVA test conducted on all conditions showed significant difference in EMG (MEPs, RMSs) responses ($\chi^2(1) = 32.641$, $p < 0.001$) (Figure 3). Wilcoxon post-hoc multiple comparisons showed a significant difference between nMEPs of the standard posture and of the inverse posture only for AP orientation condition (nMEP mean \pm SD: 0.528 ± 0.465 vs 0.190 ± 0.355 , $z = 3.041$, $p < 0.006$). All other comparisons were not significant after correction for multiple comparisons (nMEP PA mean \pm SD: 0.338 ± 0.537 vs 0.087 ± 0.311 , $z = 3.041$, $p = 0.144$; nMEP LM mean \pm SD: 0.283 ± 0.387 vs 0.076 ± 0.270 , $z = 2.242$, $p = 0.144$; nRMS PA mean \pm SD 0.278 ± 0.568 vs 0.055 ± 0.546 , $z = 1.477$, $p = 0.882$; nRMS LM mean \pm SD 0.589 ± 1.027 vs 0.190 ± 0.404 , $z = 1.964$, $p = 0.300$; nRMS AP mean \pm SD 0.720 ± 0.948 vs 0.267 ± 0.464 , $z = 1.999$, $p = 0.276$) (Figure 3). Regarding paired-pulse protocols, Wilcoxon signed-rank test on conditioned MEPs (SICI) vs test MEPs showed that inhibition was effectively induced in all hand postures (*SICI standard* inhibition: 34%; conditioned MEP mean \pm SD: $1.920 \text{ mV} \pm 1.787$; test MEP mean \pm SD: $2.909 \text{ mV} \pm 1.585$, $z = 2.659$, $p = 0.006$); (*SICI inverse* inhibition: 31%; conditioned MEP mean \pm SD: $1.437 \text{ mV} \pm 0.730$; test MEP mean \pm SD: $2.379 \text{ mV} \pm 1.064$, $z = 3.285$, $p < .001$); (*SICI intermediate* inhibition: 42%; conditioned MEP mean \pm SD: $1.430 \text{ mV} \pm 1.194$; test MEP mean \pm SD: 2.372 ± 1.482 , $z = 3.563$, $p < .001$) (Figure 4a). Wilcoxon signed-rank test did not find significant difference between nSICI of

standard posture and nSICI of inverse posture ($nSICI$ standard mean \pm SD: $7\% \pm 0.37$; $nSICI$ inverse mean \pm SD: $10\% \pm 0.42$, $z=-0.052$, $p=0.973$) (Figure 4b).

Wilcoxon signed-rank test on conditioned MEPs (ICF) vs test MEPs showed that excitation was effectively induced in the standard posture (ICF standard excitation: 21%; conditioned MEP mean \pm SD: $3.471 \text{ mV} \pm 1.994$ vs $2.909 \text{ mV} \pm 1.585$, $z = -2.485$, $p=0.011$) and in the inverse posture (ICF inverse excitation: 34%; conditioned MEP \pm SD: $3.082 \text{ mV} \pm 1.430$ vs $2.379 \text{ mV} \pm 1.064$, $z = -3.007$, $p<.001$) but not in the intermediate posture (ICF intermediate excitation: 42%; conditioned MEP \pm SD: $2.573 \text{ mV} \pm 1.571$ vs $2.372 \text{ mV} \pm 1.482$, $z = -0.608$, $p=0.562$) (Figure 4a). At the t-test, no significant differences were found between nICF of standard posture and nICF of inverse posture ($nICF$ standard mean \pm SD: $7\% \pm 0.55$; $nICF$ inverse mean \pm SD: $21\% \pm 0.47$, $z=-1.408$, $p=0.197$) (Figure 4c).

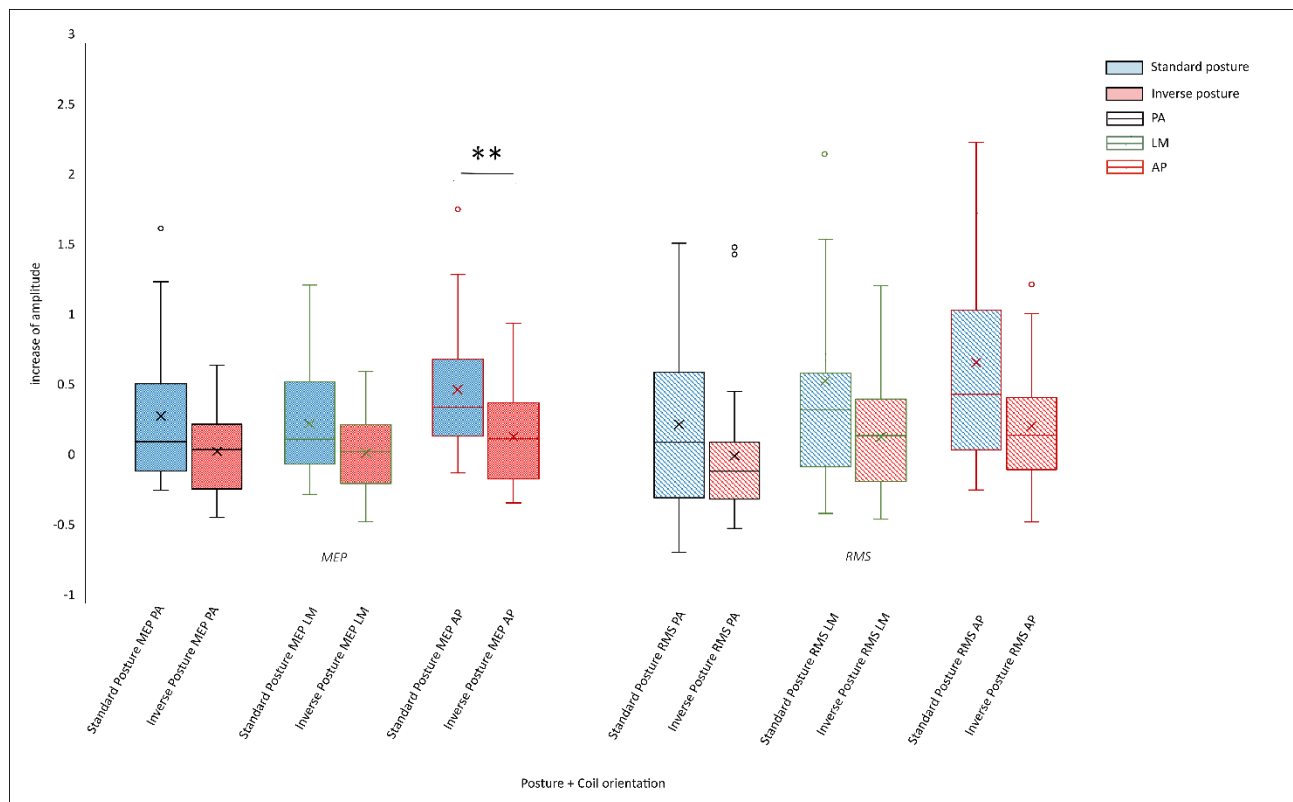


Figure 3, Posture advantage in Motor evoked potentials (MEPs) and Root mean squares (RMSs). Box and whisker plots of motor evoked potentials (MEPs) and root mean square responses for basal tone (RMSs) expressed in relative increases with respect to intermediate posture: the rectangle (box) represents the second and the third quartiles, the central horizontal line indicates the median values. The lines (whiskers) extending from the box indicate variability outside the lowest and the upper quartiles. The values below the inferior and above the superior limits are considered outliers (circles). The inferior limit is equal to the first quartile minus 1.5 times the interquartile range, the superior limit is equal to the third quartile plus 1.5 times the interquartile range. Crosses indicate mean values. Asterisks with line indicates significant difference among conditions: $***p < .001$, $**p < .01$.

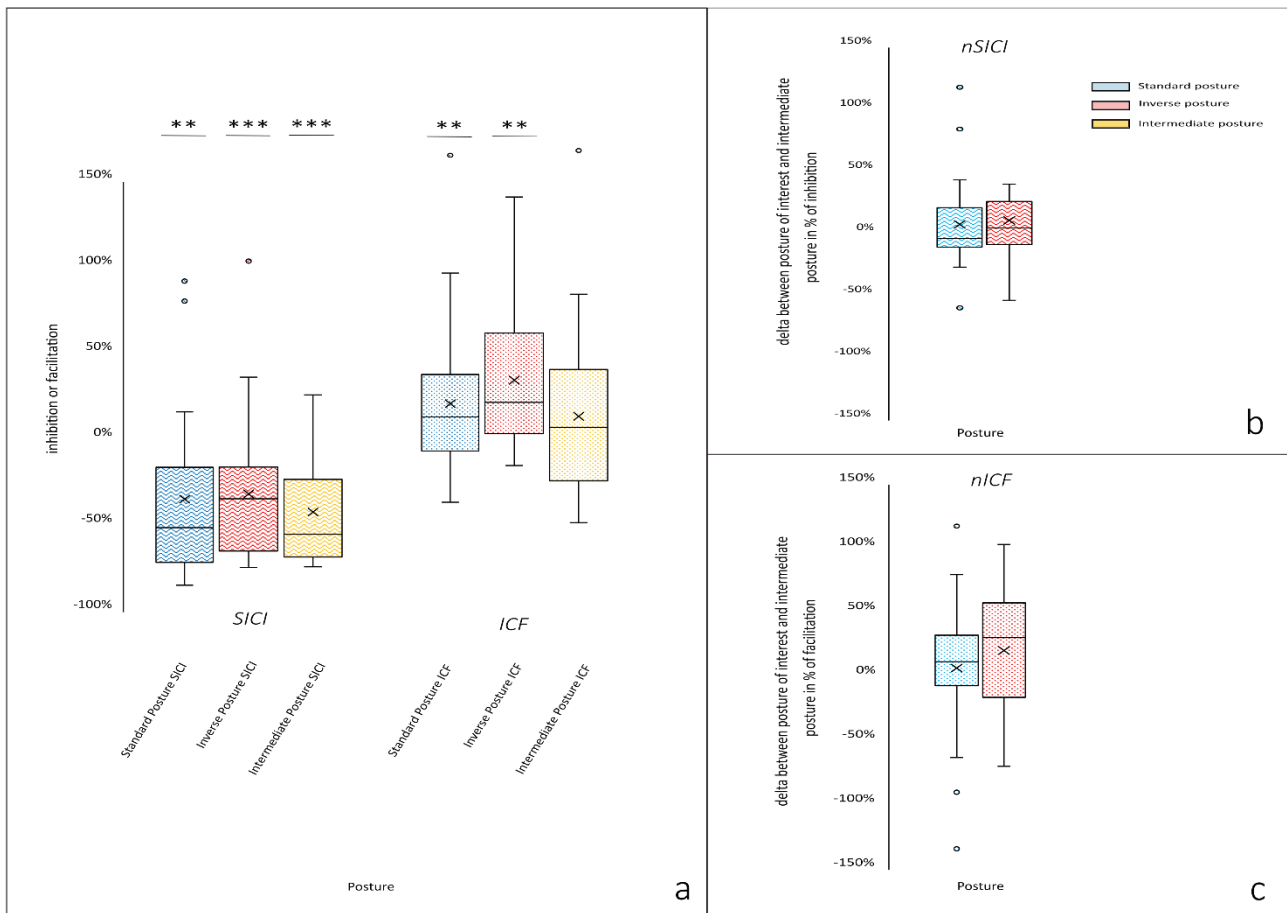


Figure 4, Inhibition (SICI) and facilitation (ICF) in postures. a) Box and whisker plots of percentage of inhibition or facilitation for all the postures respect to non-conditioned MEPs. b) Box and whisker plots of delta in percentage of inhibition between standard or inverse posture and intermediate one. c) Box and whisker plots of delta in percentage of excitation between standard or inverse posture and intermediate one. The rectangle (box) represents the second and the third quartiles, the central horizontal line indicates the median values. The lines (whiskers) extending from the box indicate variability outside the lowest and the upper quartiles. The values below the inferior and above the superior limits are considered outliers (circles). The inferior limit is equal to the first quartile minus 1.5 times the interquartile range, the superior limit is equal to the third quartile plus 1.5 times the interquartile range. Crosses indicate mean values. Asterisks represent statistical significance of percentage of inhibition or facilitation with respect to the non-inhibited MEP: *** $p < .001$, ** $p < .01$. The absence of asterisks in panel B and C indicates that no statistical difference was found between conditions.

3.5 Discussion

Recent studies showed that body representation stores a ‘canonical’ hand configuration which facilitates both sensory (Romano et al., 2017) and action processing (Romano et al., 2021) (Romano et al., 2019), defined as standard posture. Previously, the standard posture has been shown to offer advantages in terms of quicker reaction time, potentially resulting from reduced action computation time. It has also been associated with increased cortical excitability, likely attributed to the prioritised activation of M1 (Romano et al., 2021). Furthermore, improved sensory discrimination performance has been observed, possibly due to reduced processing time for spatial information from sensory inputs in this posture (Romano et al., 2017). All the described advantages may be imputed to an overlapping between the standard and the actual posture.

Spreading of the advantage of standard posture to sensory and motor domains suggests that this is computed at a hierarchically higher level than unimodal somatosensory or motor body representations. However, no studies investigated the specific cortical circuits involved in the computational advantage of the standard posture.

With such aim, here we compared MEP amplitudes evoked by different TMS coil orientations (postero-anterior or PA, latero-medial or LM, antero-posterior, AP) during different hand postures, because different coil orientations preferentially activate different cortical circuits. LM is thought to directly activate the pyramidal tract (Di Lazzaro et al., 2012), while AP to mainly do it indirectly through the activation of higher-level circuits (Di Lazzaro & Rothwell, 2014). Considering the supra-ordinated quality of the standard posture advantage, we expected that the difference in cortical excitability between postures was better highlighted by the AP coil orientation than by LM or PA orientation. In our prior findings, a statistically significant difference was observed between postures when considering the PA orientation. Notably, when refraining from applying multiple comparison corrections, a comparable outcome persists also in our analysis. The fact that, with multiple comparison adjustments, the difference between the two postures does not reach statistical significance is not in contrast with our hypothesis. Indeed, it highlights that although the difference exists at all levels, it is only at the AP level that we can pinpoint the source of the computational advantage. While PA recruits only M1 neurons, the current induced in M1 by AP orientation is thought to activate cortico-cortical fibres originating from PM cortex (Di Lazzaro & Ziemann, 2014). This lies in the fact that the smaller and delayed late I-waves evoked by AP magnetic stimulation resemble the waves evoked in M1 of monkeys after ventral PM cortex stimulation (Shimazu, Maier, Cerri, Kirkwood, & Lemon, 2004). In humans, a similar physiological process may account for the I-waves dispersed activity evoked by AP orientation suggesting the recruitment of inputs from

premotor areas to M1 (Di Lazzaro & Rothwell, 2014). Consistently with the proposed hypothesis, our findings showed a significant difference between the standard and the inverse posture only with AP TMS, supporting the possible origin of the postural advantage in a circuit including M1 and PM areas (Di Lazzaro & Rothwell, 2014). PM cortex is involved in body representation related functions such as multisensory description of limb position (Lloyd, Shore, Spence, & Calvert, 2003), feeling of ownership (Ehrsson, Spence, & Passingham, 2004) and sense of agency (Abdulkarim, Guterstam, Hayatou, & Ehrsson, 2023). Most important, PM cortex plays a crucial role in determining M1 activity; during motor planning, a set of motor commands are generated on the bases of different hierarchical representations of actions (Grafton, 2010). Control of different aspects of action is implemented by different sub areas: dorsal premotor cortex in reaching (Takahashi et al., 2017) and lifting movements (Davare, Andres, Cosnard, Thonnard, & Olivier, 2006), whereas the ventral one (PMv) has been associated with grasping (Davare et al., 2006), object manipulation (Vingerhoets, Nys, Honoré, Vandekerckhove, & Vandemaele, 2013), action observation and motor imagery (Hardwick, Caspers, Eickhoff, & Swinnen, 2018). Thus, considering PMv involvement in performing the precision grip posture (Davare, Kraskov, Rothwell, & Lemon, 2011; Davare, Montague, Olivier, Rothwell, & Lemon, 2009; Davare, Rothwell, & Lemon, 2010) it is plausible for this area to play a major role in the computational advantage. In our previous work, involving neutral tasks, we showed that the standard posture is facilitated regardless of action goals (Romano et al., 2021). Accordingly, although PMv has been widely shown to be involved in grip shaping depending on object affordance and overall goal of the action, recent evidence suggested a general role in hand shaping for gesture without the presence of objects (Reader & Holmes, 2018). In line with this, we do not impute the differences in excitability between postures to a PMv-M1 interaction which is muscle specific (Davare et al., 2009), but we claim that the advantage is not due to different ongoing muscular activity (Romano et al., 2021).

Our results suggest that PMv is either the source or a key element of the network computing the internal model for the standard posture, which probably involves parietal and other high-order areas (Davare et al., 2011). Given that the standard hand posture is facilitated both in sensory and motor signals computation, one might speculate the engagement of cortical circuit from other body-related areas, such as the parietal cortex (Berlucchi & Aglioti, 2010), which is implicated together with PMv in multisensory representations of limb position (Limanowski & Blankenburg, 2016), or the lateral posterior temporal cortex which has a pivotal role in conceptual aspect of actions (Wurm & Caramazza, 2019). In support of such wider and higher origin, the advantage of standard posture has been reported also in semantic domains: image and words related to upper space are more associated with the ones related to the index, while image and words related to lower space with the ones related

to thumb (Romano et al., 2017). Further studies are needed to clarify the specific contributions of such areas in the standard posture advantage. For instance, specific techniques of functional connectivity may be employed to investigate how strongly they communicate with M1 and with each other when either one or the other posture is used.

Thus, the evidence reported in this work strongly supports the hypothesis that the postural advantage comes from an extraneous source than M1. In favour of this, SICI and ICF reported no differences in inhibition or facilitation between hand postures. Although previous studies about the effect of voluntary contraction in inhibition and facilitation of M1 showed that both inhibitory and facilitatory circuits become less excitable with sustained muscular contraction (Hunter, McNeil, Butler, Gandevia, & Taylor, 2016; Ridding, Taylor, & Rothwell, 1995), we found a significant effect of the dual stimulus protocols for both the standard and the inverse posture. This finding implies that the absence of significant difference in inhibition/facilitation between the postures may not be attributable to the inefficacy of the protocols themselves. Instead, considering the association between SICI and ICF with M1 activity, it suggests that M1 is not the main determinant of the standard posture. Thus, PMv may fulfil this modulatory role, by facilitating the standard posture over the inverse one. Although the reason behind the standard posture remains unknown, we previously hypothesised that, from arboreal locomotion to dexterous movements, the advantage of the grip may have contributed to the development of human manipulation (Romano et al., 2021). Moreover, this posture might not be the only one embedded in an a-priori representation. In a broader view, a template for action could be extended to the entire body. The previously mentioned study relative to the perceived position of the body during the anaesthesia induction (Bromage & Melzack, 1974a), reported a specific body posture which could indicate alert or protection. These specific limb positions may have been selected throughout evolution with the aim of preserving the integrity of the body by facilitating feeding or defence against predators. Such highly functional value would explain the pervasive nature of this representation.

3.6 Conclusions

The purpose of the present study was to investigate the cortical circuits involved in the standard posture representation and responsible of its computational advantage. The findings supported the hypothesis that the advantage originates from PM cortex, which, by shaping M1 activity, may play a crucial role in facilitating the standard posture. No differences in intracortical M1 inhibition or facilitation was found between postures, suggesting that the examined postural advantage is not primarily determined by M1 and, thus, confirming that the phenomenon originates from

hierarchically higher cortical regions. Overall, this study contributes to our understanding of the cerebral circuits involved in hand representation. Specifically, knowing the brain network responsible for the standard posture, may provide novel therapeutical approach to motor recovery. For example, following neurological conditions, it may be possible to target these circuits by neurostimulation interventions to enhance the effectiveness of physical rehabilitation or prostheses training.

4 Experiencing an elongated limb in virtual reality modifies the tactile distance perception of the corresponding real limb

4.1 Introduction

Sensory feedback is exploited to experience the environment and guides physical interaction. In a nutshell, sensing is the translation into neural code of parameters, which to be measured require unit of measure and a reference frame to which compare the measure. Especially, when the environment is experienced through our body (i.e., in somatosensation), it has been suggested that the reference frame we employ is our body and its metric properties (Harris et al., 2015; Proffitt & Linkenauger, 2013). This hypothesis is sound because it has been widely shown that the brain integrates a higher-order reconstruction of the body that is an implicit model of its metric properties (Longo & Haggard, 2010; Longo & Haggard, 2012), namely the *body schema* (de Vignemont, 2010), and of the space where the interaction occurs.

In touch, the perception of the distance between two stimulated points, i.e., tactile distance perception (TDP), depends on the part of the body which is stimulated. Such phenomenon, known as the Weber illusion (Weber, 1996), is certainly linked to the different tactile receptor density of different body parts, but there is more: for instance, a tactile receptor density variation of 340% results in a variation of only 30% in TDP between the palm of the hand and the forearm (Green, 1982; Weinstein, 1968). Hence, besides receptor density, which should account for coding the distance between the two stimulated points in the primary somatosensory cortex, a subsequent neural process must be involved in the Weber illusion. This process is a rescaling operation to compensate for the different receptor density, and it is likely to be based on a representation of the body parts in the body schema. Furthermore, since the body schema is continuously updated by multimodal sensory input (de Vignemont, 2010; Romano et al., 2021; Serino & Haggard, 2010) we hypothesise that a modification of the body schema achieved through multisensory feedback modulation would induce a consequent change of the tactile perception of the distance. It has indeed been previously shown that by visually deforming the hand and forearm with magnifying and reducing lenses for about 1 hour, the TDP relative to the participant's forearm would change with respect to the not altered control part (Taylor-Clarke, Jacobsen, & Haggard, 2004). In another experiment inspired by the Pinocchio illusion (Lackner, 1988), the proprioceptive illusion of an elongation of the index finger significantly increased the TDP on the same finger. The illusion of finger elongation was achieved by stimulating

the spindles of the right arm biceps with a vibrator placed on the tendon (known as tendon-vibration illusion) while participants held their left index finger with their right arm (de Vignemont, Ehrsson, & Haggard, 2005). Those studies confirmed that the perceived size of the body impacts on TDP, which is in line with the hypothesis of the body schema acting as reference frame for touch.

Another strategy to modify the perceived size of the body exploits the embodiment of fake hand through the rubber hand illusion (RHI) paradigm (Botvinick & Cohen, 1998), while the fake hand is placed in an artificial position, farther than the real hand, inducing the illusory feeling of having a longer arm. This has been demonstrated both in real and in virtual environment (Armell & Ramachandran, 2003b; Kalckert, Perera, Ganesan, & Tan, 2019b; Kilteni, Normand, Sanchez-Vives, & Slater, 2012c)

However, to our knowledge, no previous study has investigated the possible change in tactile distance perception following a modification of the body schema through the embodiment of a fake limb. Such insight could add up to the current knowledge on the effects of embodiment of foreign body parts on perception.

Thus, we used a RHI paradigm in virtual reality, a Virtual Hand Illusion (VHI), with an elongated virtual forearm to induce in participants the feeling of owning such a distorted limb and investigated the evolution of the TDP on the corresponding real body part following different forearm elongations. We hypothesised that the synchronous brush-stroking of a hand at the end of an elongated forearm would have increased the TDP on the corresponding real forearm and that the variation in TDP would have positively correlated with the amount of forearm elongation and with the achieved level of embodiment of the hand. The asynchronous stimulation of a hand at the end of an elongated forearm has been acquired as control condition.

4.2 Materials and methods

Participants

Sixty-nine participants (33 females, 6 left-handed, aged 23.9 ± 5.6) were enrolled in the study. For one of our analyses, participants were divided into three independent groups, depending on the first condition they would undergo (three conditions tested), thus each group containing twenty-three participants (see Analysis for detailed explanation). This number of enrolled participants per group has been based on the TDP task (TDPT) data distribution from the study of Taylor-Clarke and colleagues (Taylor-Clarke et al., 2004) to show a 7% mean shift in TDP between pre and post VHI, achieving an effect size of 0.32, a power superior to 0.8 and considering an independent t-test. All participants reported to have normal tactile sensation of the hand, forearm, and forehead, and normal

or corrected-to-normal vision. All participants provided written informed consent before the experiment in accordance with the Declaration of Helsinki and following amendments. The experiment was conducted after approval of the local Ethics Committee (EMBODY protocol).

Setup

Participant sat comfortably on a chair in front of a table placed within a 2.40m x 2.00m x 1.80m metallic structure. A large paper goniometer (58cm radius) was displayed upon the table. Participants visualized the immersive virtual environment through a virtual reality (VR) system (HTC Vive, HTC Corporation). They wore a VR headset (head mounted device – HMD) and the HMD movement was tracked by two infrared cameras (base-stations). To enhance the immersion of participants inside the virtual environment and their sense of agency over the virtual upper limb, the movements of their real left arm, forearm, hand, and fingers were tracked by motion capture systems. Arm and forearm movements were tracked with four infra-red cameras (Optitrack 13W, Natural Point, Inc) and reflective optical markers worn by the participant, whereas finger and hand movements were tracked by a dedicated infra-red motion tracking device attached on the HMD (Leap Motion, Ultraleap). We developed a VR environment (using the game engine Unity, version 2018.3.0, Unity Technologies) which replicates the lab room where the experiment was run, including the table and the chair. In the virtual environment, participants saw in a first-person perspective (1PP) their avatar's body (male or female) sitting in front of the virtual table. In the default position, both the participant and their avatar had the left forearm (palm down) on the table and the right arm alongside the body. The left forearm of the participant avatar could be elongated by different lengths (20cm or 40cm depending on the condition). The real experimenter, located in front of the participant, stimulated the participant's left hand index finger with a paintbrush. Both the experimenter and the paintbrush movement were replicated in the virtual environment (Figure 5). The virtual avatars were created with the open-source software MakeHuman™.

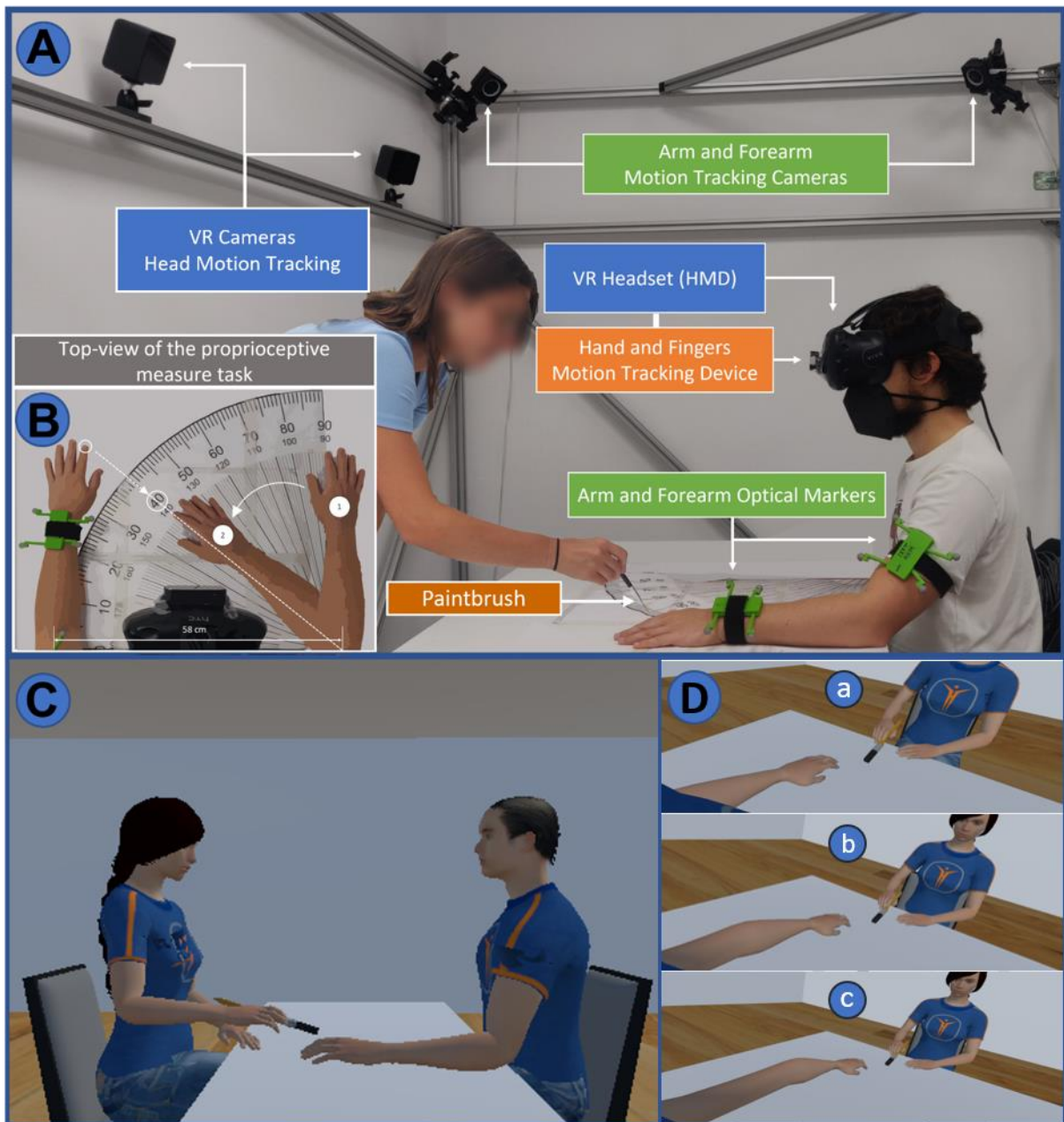


Figure 5, Real world and virtual experimental setup. A) Experimental setup with experimenter (left) and participant (right) in default position. B) Proprioceptive drift measurement technique. C) Virtual Environment – Sideview. Virtual experimenter (left) holding the paintbrush and participant avatar (right) in default position, without forearm elongation. D) Virtual Environment – Participant’s IPP. Without forearm elongation (a), with 20cm elongation (b), with 40cm elongation (c).

Experimental protocol

We investigated the effects of a VHI with an elongated virtual forearm on TDP under three conditions (Figure 6). Synchronous VHI were performed with the virtual forearm elongated by 20cm (20S) or 40cm (40S), whereas an asynchronous VHI with a 20cm forearm elongation (20A) was used as control condition. Firstly, the virtual environment was turned pitch black, and participants underwent a preliminary task of TDP (pre-TDPT) to measure their baseline TDP (see section Measures for detailed information). Then, when VR was activated, participants were instructed to look at their surroundings (moving only their head) to familiarize with the virtual environment. To give participants agency over the avatar, they were asked to move their left arm for ninety seconds and then their hand and fingers for additional ninety seconds while looking at their virtual counterparts which moved accordingly.

Finally, participants were instructed to place back their left arm in the default position, and to keep it still until further notice. The VR environment was turned pitch black. Participants then performed a proprioceptive measure (pre-PM), in which they had to indicate the felt position of the tip of their left index finger (see section Measures for detailed information). The left virtual forearm was then elongated by 20cm or 40cm depending on the condition. The virtual environment was illuminated again, and participants were asked to look at and pay close attention to the (virtual) hand. To perform the VHI, the experimenter started the brush stroking synchronously or asynchronously (depending on the condition) with respect to the visual virtual brush stroking performed by the virtual experimenter on the left index finger of the participant avatar. Brush stroking lasted ninety seconds. Following the VHI, another proprioceptive measure (post-PM) was immediately performed, followed by a post-TDPT. Participants then were asked to answer a questionnaire evaluating the strength of the embodiment illusion elicited by the VHI. The latest steps, starting from the proprioceptive measure prior to the VHI, were repeated for every VHI condition, and conditions were tested in a pseudo-random order among participants. The whole procedure, including the preparation of the participant, lasted around one hour and half.

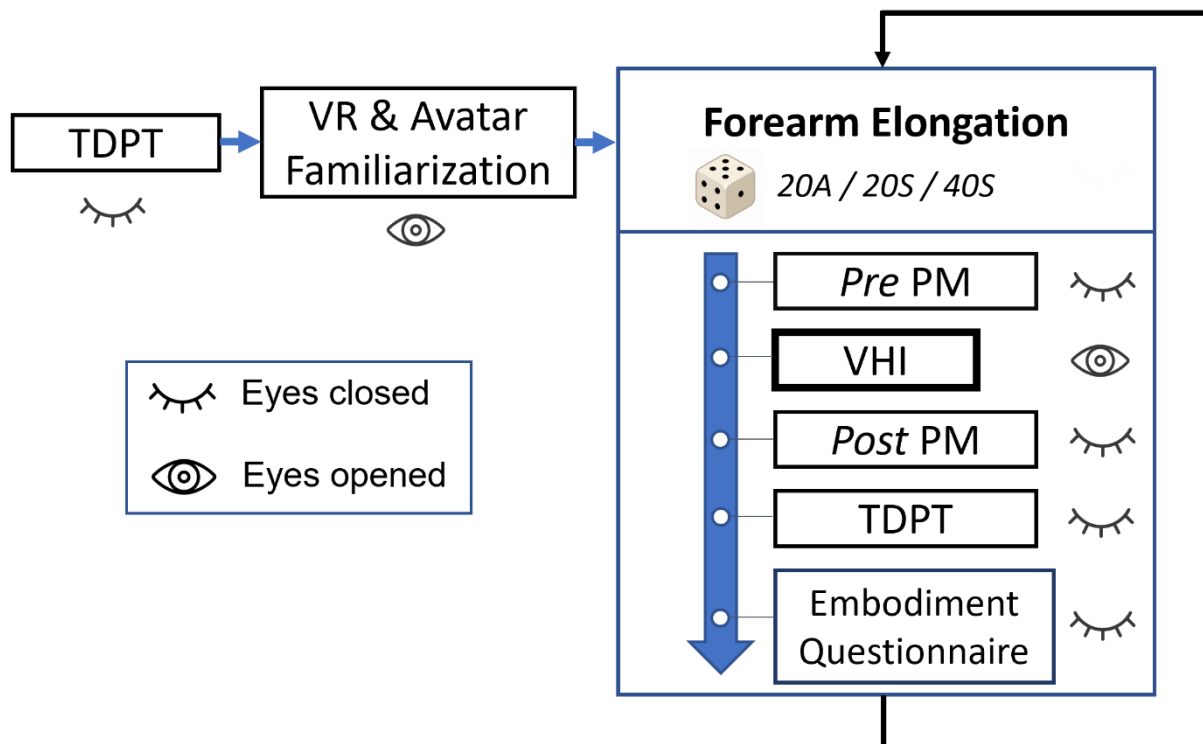


Figure 6, Experimental protocol.

Measures

To measure the embodiment outcomes following the VHI, participants were asked to fill a self-evaluation questionnaire adapted from Botvinick & Cohen (Botvinick & Cohen, 1998; D’Alonzo, Mioli, Formica, Vollero, & Di Pino, 2019) to evaluate the strength of the ownership illusion over the virtual hand (Figure 7). Three of the statements (Figure 7: Q1, Q2 and Q3) were ownership-related and referred to the extent of sensory transfer into the virtual hand and its self-attribution during the VHI. The six other statements (Figure 7: Q4, Q5, Q6, Q7, Q8 and Q9) served as control items to assess compliance, suggestibility, and placebo effect. For each statement, participants were asked to rate the extent to which these statements did or did not apply to their experience, by using a seven-point Likert scale. On this scale, -3 meant: "I am absolutely certain it did not apply", 0 meant: "uncertain whether it applied or not" and +3 meant: "I am absolutely certain it applied". The statements were presented to participants in a random order. The embodiment outcome of the VHI was taken from the questionnaire results and computed as the RHI Index. The RHI Index is defined as the difference between the mean score of the ownership statements and the mean score of the control statements (Abdulkarim & Ehrsson, 2016). The greater the RHI Index, the stronger the perceived embodiment.

VHI Embodiment Questionnaire		
Embodiment Statements	Q1	It seemed like I felt the touch of the paintbrush on the spot on which I was seeing the hand being touched.
	Q2	It seemed like the touch I was feeling were due to the touch of the paintbrush on the hand I was seeing.
	Q3	It felt like the hand I was seeing were my own hand.
Control Statements	Q4	It felt like my real hand were moving towards the hand I was seeing.
	Q5	It felt like I had three arms or three hands.
	Q6	It felt like the touch I was perceiving were coming from somewhere between my hand and the hand I was seeing.
	Q7	It felt like my real hand were turning virtual.
	Q8	It felt like the hand I was seeing was moving towards my real hand.
	Q9	The hand I was seeing was starting to look like my real hand, in terms of shape, skin tone, freckles, or other characteristics.

Figure 7, Embodiment questionnaire with embodiment and control statements.

To measure the proprioceptive drift (PD) caused by the VHI (Botvinick & Cohen, 1998), participants were helped placing their right arm on the paper goniometer, parallelly to the left arm, in the starting position (90°). Participant forearms were always positioned on the extremities of the goniometer so that their elbows in-between distance would be of 580mm (see Figure 7B). They were instructed to point with their right index finger towards the felt position of the tip of their left index finger by flexing the right forearm while keeping forearm, hand and finger along a straight line (Figure 7B). We collected the corresponding angle and helped participants placing their right arm back alongside their body. Angular values were converted into the left elbow-index perceived distance expressed in millimeters, using a simple trigonometric function to obtain the elbow-index distance corresponding to the given angular value (θ) (eq. 1.1). The proprioceptive measure (PM) was performed right before (pre-PM) and after (post-PM) every VHI and the resulting PD was calculated as the difference between the post-PM and the pre-PM (eq. 1.2).

$$PM = 580 \times \tan(\theta) \quad (1.1)$$

$$PD = PM_{post} - PM_{pre} \quad (1.2)$$

To measure the TDP, participants underwent a TDPT. During the TDPT, blindfolded participants received fifty-six couples of tactile stimulation: one on the forearm (investigated TDP), and one on the forehead (used as reference TDP) in a random order. Tactile stimulations were performed using fork-like tools composed of two blunt tips with a specific distance between each other (Figure 8).

After each couple of stimulation, participants were asked to report in which of the two stimulations the distance between the tips of the forks was felt larger: they were instructed to answer “one” if the first stimulation was felt larger, “two” if it was the second. We recorded the corresponding body part on which the stimulation distance was felt larger. Distances between the tips of the forks were chosen based on a previous study using a similar task (Taylor-Clarke et al., 2004). In all couples of stimulations, we used a reference fork 45mm wide, and a fork with 30mm, 35mm, 40mm, 45mm, 50mm, 55mm or 60mm between-tips distance. The order, body part, and distance of the stimulations were randomised and balanced among the fifty-six couples of stimulations (twenty-eight unique couples of stimulations, each one performed twice, see Figure 8).

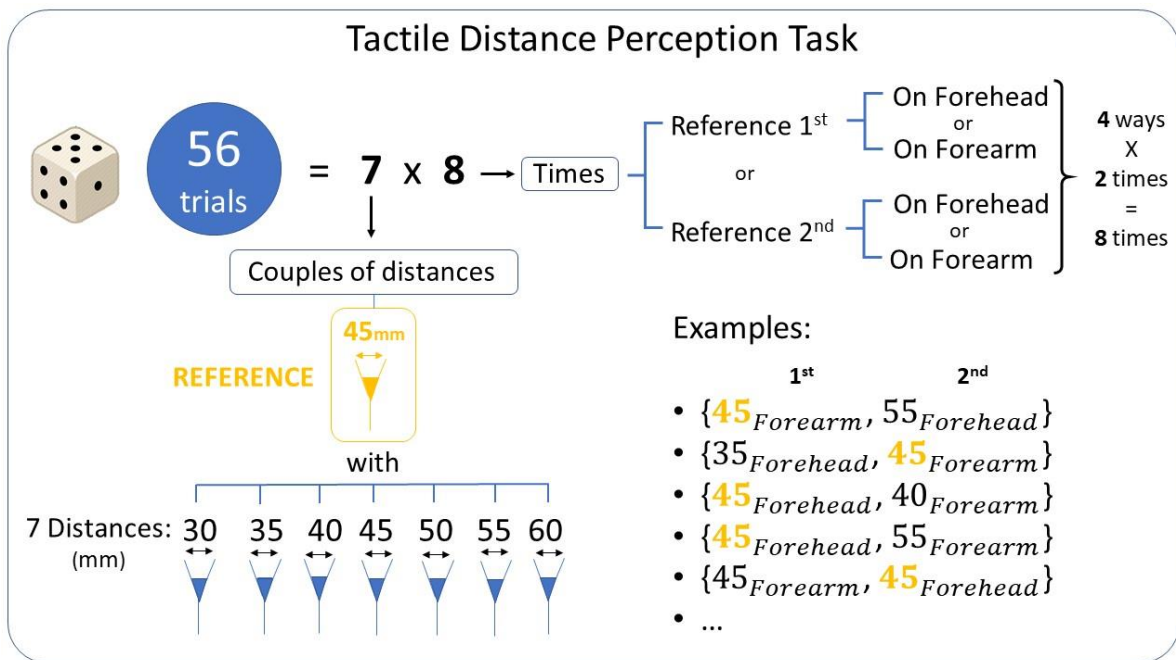


Figure 8, Tactile Distance Perception Task. 7 couples of distances tested in 4 different ways (28 different trials); each way repeated twice: 56 trials in total.

From the participants responses, we calculated the percentage of "forearm" answers (%FA) for each difference (ΔL) between the length of the forearm stimulation ($L_{forearm}$) and the length of the forehead stimulation ($L_{forehead}$), positive values meaning bigger distance administered to the forearm (eq. 2).

$$\Delta L = L_{forearm} - L_{forehead} \quad (2)$$

$$\Delta L \in \{-15, -10, -5, 0, 5, 10, 15\}$$

The TDP was measured by the Point of Subjective Equality (PSE). In this study, the PSE is defined as the ΔL value (extra-distance between-tips on the forearm stimulation compared to the forehead stimulation) at which the between-tips distances of both stimuli are *felt* as equal. Thus, since for an

equal tactile distance, TDP is greater on the forehead than on the forearm (greater tactile receptor density on the forehead), an augmentation of the TDP on the forearm would result in reduction of the PSE. It was measured in millimeters. To calculate the PSE, we proceeded as follows: for every participant and every TDPT (Pre, 20A, 20S, 40S) we plotted (Figure 9) the %FA (y-axis) in function of the ΔL (x-axis) as independent variable and fitted the data distribution with the following psychophysics sigmoid function (eq. 3.1):

$$P(\Delta L, PSE, EA) = \frac{100}{1 + \exp\left(-\frac{\Delta L - PSE}{0.5 \times EA}\right)} \quad (3.1)$$

adapted from (Di Pino et al., 2020a) where P is the probability (expressed as a percentage) of feeling the larger stimulation of the forearm. From the plotted curve (Figure 9), the PSE can be defined as:

$$PSE = \Delta L|_{P_{50\%}} \quad (3.2)$$

It represents the ΔL value of the point in which the curve corresponds to the $P = 50\%$ value, i.e., the ΔL value for which the participant has the same probability to perceive the larger stimulation on the forearm as on the forehead (perceived equality of distances). EA is the esteem accuracy and represents the ΔL value of the point in which the line tangent to the curve at the point of coordinates (PSE, 50%) reaches the value $P = 100\%$, subtracted by the PSE value. It is the inverse of twice the slope of the curve at (PSE, 50%). Considering that we expected a change in TDP and not in tactile accuracy, the EA was not further considered in the study. PSE values were obtained from the fittings results. The goodness-of-fit (R-squared) of all analysed participants was above 0.6 (moderate effect size) (Moore, Notz, & Fligner, 2013).

Then, we computed for each condition the variation of PSE, i.e., ΔPSE , the difference between the post-PSE (after the VHI) and the pre-PSE (baseline PSE for the first tested condition and PSE after the previous condition for following conditions).

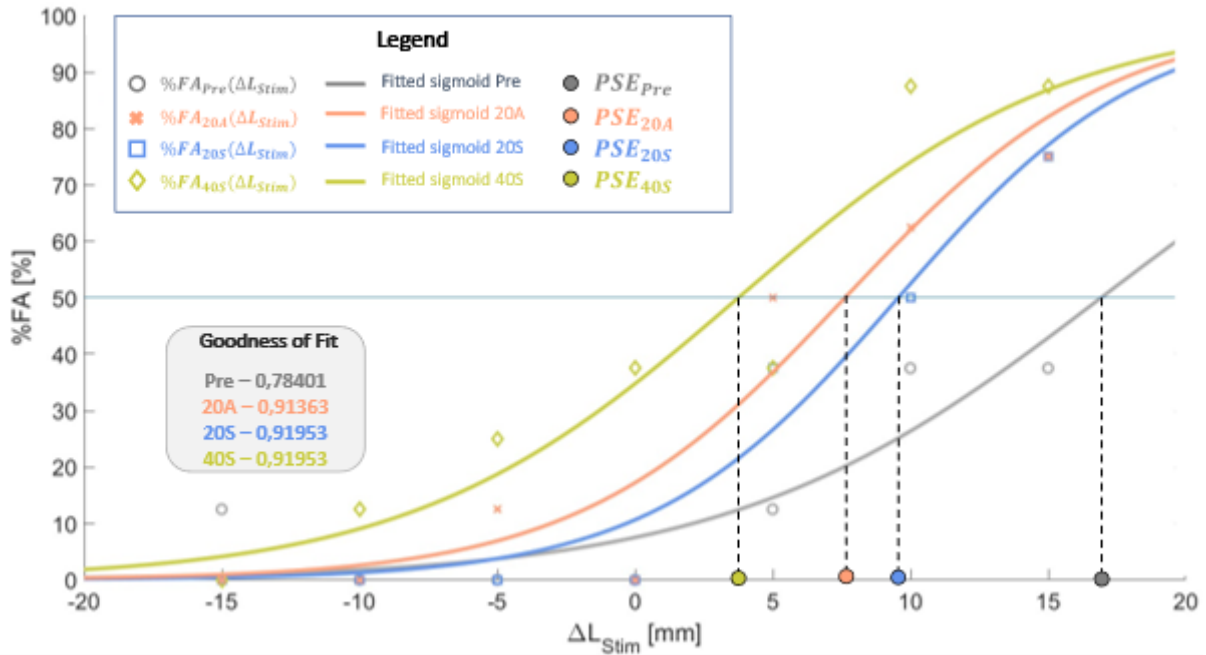


Figure 9, Example of a typical TDPT results plot for one subject. Raw results are the percentages of "forearm" answers in function of stimulation distance difference between the stimulation on the forearm and the stimulation on the forehead (ΔL). They are identified with grey empty circles (Pre), red crosses (20A), blue squares (20S), and green diamonds (40S). Continuous curves are their color-corresponding fitted sigmoid curves with their goodness-of-fit values specified in the top-left-hand corner. Filled circles on the abscise indicate the graphical definition of the PSE.

4.3 Analysis

Two separate analyses were planned. The general analysis was a within-subjects analysis (i.e., repeated measures). However, we considered the possibility that by undergoing different conditions successively without a pause between them, one condition could have an influence on the successive one and that by repeating the VHI, its intensity might decrease. Therefore, to discard these possible effects from the analysis, a between-subject analysis was planned regarding the data relative to the first condition presented to participants only. Thus, three independent groups (of 23 subjects each) were formed depending on the first condition tested. In both analyses, the significance threshold was set to p-values lower than 0.05 for all statistical tests. Correlation analyses were performed between RHI Index and ΔPSE and between PD and ΔPSE .

General analysis

For each condition, all data (RHI Index, PD and ΔPSE) were distributed normally (Shapiro-Wilk test, $p > 0.05$). We used pre-planned Student's paired t-tests to evaluate the effects of the VHI *synchronicity* (20S vs 20A) and forearm *elongation* (40S vs 20S) on RHI Index, PD and ΔPSE (Bonferroni corrected for two comparisons). We tested the significance of the variations of PD and ΔPSE with

respect to 0 using one-sample Student t-tests. To investigate any difference of distribution in *pre* measures between conditions (20S vs 20A and 40S vs 20S) for the PD and Δ PSE i.e., pre-PM and pre-PSE, we used Student's paired t-tests on pre-PM data (normally distributed among conditions, Bonferroni corrected for two comparisons) and Wilcoxon's signed-ranked t-tests on pre-PSE data (non-normally distributed among conditions, Bonferroni corrected for two comparisons). For correlation analysis, Spearman's ρ was calculated between RHI Index and Δ PSE. Pearson's r was calculated between PD and Δ PSE.

First condition analysis

Among each group, all data (RHI Index, PD, Δ PSE) were normally distributed (Shapiro-Wilk test, $p > 0.05$). We used pre-planned independent Student's t-tests to evaluate the effects of *synchronicity* (20S vs 20A) and *elongation* (40S vs 20S) on RHI Index, PD and Δ PSE (Bonferroni corrected for two comparisons). We tested the significance of the variations of PD and Δ PSE with respect to 0 using one-sample Student t-tests. Independent Student's t-tests were used to investigate any difference of distribution in pre-PM and pre-PSE data between conditions (normally distributed among conditions, Bonferroni corrected for two comparisons). For correlation analysis, Pearson's r was calculated between RHI Index and Δ PSE, Spearman's ρ was calculated between PD and Δ PSE.

4.4 Results

A summary of the results can be found in Table 1 with specific p-values and confidence intervals.

General analysis

The *synchronicity* effect was found significant on the RHI Index (Figure 10, top-left graph). Indeed, the score of the synchronous VHI (20S) resulted significantly greater than the asynchronous control condition (20A) ($t = 8.849$, $p < 0.001$). However, the *elongation* effect was not found significant (Figure 10, top-right graph): no significant difference in RHI Index score was found between the synchronous conditions 20S vs 40S ($t = 0.145$, $p = 1.000$).

Neither the *synchronicity* nor the *elongation* effect was found significant on PD (Figure 10, middle graphs; 20S vs 20A: $t = 1.941$, $p = 0.116$ and 40S vs 20S: $t = 1.132$, $p = 0.526$). Nevertheless, PD resulted significantly greater than 0 following the synchronous conditions (20S: $t = 3.035$, $p = 0.004$; 40S: $t = 3.499$, $p < 0.001$) but not following the asynchronous one (20A: $t = 0.118$, $p = 0.906$) and no significant

difference of PD pre-measures (pre-PM) was found neither between 20S and 20A ($t=-0.940$, $p=0.704$) nor between 40S and 20S ($t=0.583$, $p=1.000$).

No significant effect of *synchronicity* was found on Δ PSE (Figure 10, bottom-left graph; 20S vs 20A: $t=1.139$, $p=0.518$), nor any significant *elongation* effect (40S vs 20S: $t=-1.611$, $p=0.224$). However, Δ PSE was found significantly lower than 0 following the 40S condition but not for other conditions (Figure 10, bottom-right graph; 20A: $t=-1.717$, $p=0.091$; 20S: $t=0.316$, $p=0.753$; 40S: $t=-2.295$, $p=0.025$) and no significant difference of Δ PSE pre-measures was found neither between 20S and 20A ($z=-1.101$, $p=0.544$) nor between 40S and 20S ($z=0.186$, $p=1.000$). No significant correlation was found between any measure (Figure 12, top graphs; $\rho(\text{RHI Index}, \Delta\text{PSE})=-0.085$, $p=0.325$; $r(\text{PD}, \Delta\text{PSE})=-0.127$, $p=0.142$).

First condition analysis

The *synchronicity* effect was found significant on the RHI Index (Figure 11, top-left graph). Indeed, the score of the synchronous VHI resulted significantly greater than the asynchronous control condition (20S vs 20A: $t=3.473$, $p=0.002$) and no significant effect of *elongation* was found on the RHI Index (Figure 10, top-right graph; 20S vs 40S: $t=0.606$, $p=1.000$).

No significant difference of PD pre-measures was found between conditions (20S vs 20A: $t=-0.004$, $p=1.000$ and 40S vs 20S: $t=1.063$, $p=0.588$) and all conditions were found to elicit a PD significantly higher than 0 (Figure 11, middle line graphs; 20A: $t=2.737$, $p=0.012$; 20S: $t=3.547$, $p=0.002$; 40S: $t=3.116$, $p=0.005$). However, no significant effect of *synchronicity* nor *elongation* was found on PD (20S vs 20A: $t=0.770$, $p=0.892$; 40S vs 20S: $t=-0.999$, $p=0.646$).

No significant difference of Δ PSE pre-measures was found between conditions 20S and 20A ($t=1.463$, $p=0.302$) nor between 40S and 20S ($t=1.029$, $p=0.620$). All conditions were found to elicit a Δ PSE significantly lower than 0 (Figure 11, bottom line graphs; 20A: $t=-2.608$, $p=0.016$; 20S: $t=-2.288$, $p=0.033$; 40S: $t=-6.232$, $p<0.001$). No significant effect on *synchronicity* was found on Δ PSE (20S vs 20A: $t=0.096$, $p=1.000$), but the *elongation* effect was significantly present (40S vs 20S: $t=-2.551$, $p=0.030$). The correlation between RHI Index and Δ PSE was found close to significance (Figure 12, bottom-left graph; $r=-0.225$, $p=0.069$) and no significant correlation was found between PD and Δ PSE (Figure 12, bottom-right graph; $\rho(\text{PD}, \Delta\text{PSE})=0.116$, $p=0.353$).

Statistical Table

Figure	Graph	Data structure	Type of test	p-values	95% C.I. for Cohen's d
Figure 10	Top-left	Normal distribution	Paired Student's t-test; Bonferroni corrected for two comparisons	< 0.001	0.767 to 1.359
Figure 10	Top-right	Normal distribution	Paired Student's t-test; Bonferroni corrected for two comparisons	1.000	-0.219 to 0.253
Figure 10	Middle-left	Normal distribution	Paired Student's t-test; Bonferroni corrected for two comparisons	0.116	-0.008 to 0.534
Figure 10	Middle 20A	Normal distribution	One-sample Student's t-test vs 0	0.906	-0.251 to 0.283
Figure 10	Middle 20S	Normal distribution	One-sample Student's t-test vs 0	0.004	0.133 to 0.689
Figure 10	Middle 40S	Normal distribution	One-sample Student's t-test vs 0	< 0.001	0.192 to 0.756
Figure 10	Middle-right	Normal distribution	Paired Student's t-test; Bonferroni corrected for two comparisons	0.526	-0.115 to 0.422
Figure 10	Bottom-left	Normal distribution	Paired Student's t-test; Bonferroni corrected for two comparisons	0.518	-0.104 to 0.385
Figure 10	Bottom 20A	Normal distribution	One-sample Student's t-test vs 0	0.091	-0.458 to 0.034
Figure 10	Bottom 20S	Normal distribution	One-sample Student's t-test vs 0	0.753	-0.204 to 0.282
Figure 10	Bottom 40S	Normal distribution	One-sample Student's t-test vs 0	0.025	-0.532 to -0.036
Figure 10	Bottom-right	Normal distribution	Paired Student's t-test; Bonferroni corrected for two comparisons	0.224	-0.445 to 0.046
Figure 10	Top-left	Normal distribution	Independent Student's t-test; Bonferroni corrected for two comparisons	0.002	0.403 to 1.635
Figure 11	Top-right	Normal distribution	Independent Student's t-test; Bonferroni corrected for two comparisons	1.000	-0.402 to 0.757
Figure 11	Middle-left	Normal distribution	Independent Student's t-test; Bonferroni corrected for two comparisons	0.892	-0.362 to 0.824
Figure 11	Middle 20A	Normal distribution	One-sample Student's t-test vs 0	0.012	0.123 to 1.007

Figure 11	Middle 20S	Normal distribution	One-sample Student's t-test vs 0	0.002	0.270 to 1.196
Figure 11	Middle 40S	Normal distribution	One-sample Student's t-test vs 0	0.005	0.193 to 1.095
Figure 11	Middle-right	Normal distribution	Independent Student's t-test; Bonferroni corrected for two comparisons	0.646	-0.884 to 0.292
Figure 11	Bottom-left	Normal distribution	Independent Student's t-test; Bonferroni corrected for two comparisons	1.000	-0.556 to 0.613
Figure 11	Bottom 20A	Normal distribution	One-sample Student's t-test vs 0	0.016	-0.977 to -0.100
Figure 11	Bottom 20S	Normal distribution	One-sample Student's t-test vs 0	0.033	-0.926 to -0.040
Figure 11	Bottom 40S	Normal distribution	One-sample Student's t-test vs 0	< 0.001	-1.949 to -0.753
Figure 11	Bottom right	Normal distribution	Independent Student's t-test; Bonferroni corrected for two comparisons	0.030	-1.395 to -0.153

Table 1, Statistical table of the main analyses performed.

Statistical Table 2

Figure	Graph	Data structure	Type of test	p-values	r or ρ values
Figure 12	Top-left	Non-normal distribution (RHI Index)	Spearman's ρ	0.325	-0.085
Figure 12	Top-right	Normal distribution	Pearson's r	0.142	-0.127
Figure 12	Bottom-left	Normal distribution	Pearson's r	0.069	-0.225
Figure 12	Bottom-right	Non-normal distribution (PD)	Spearman's ρ	0.353	0.116

Table 2, Statistical table of the correlation tests performed with corresponding p-values and correlation coefficients.

General analysis

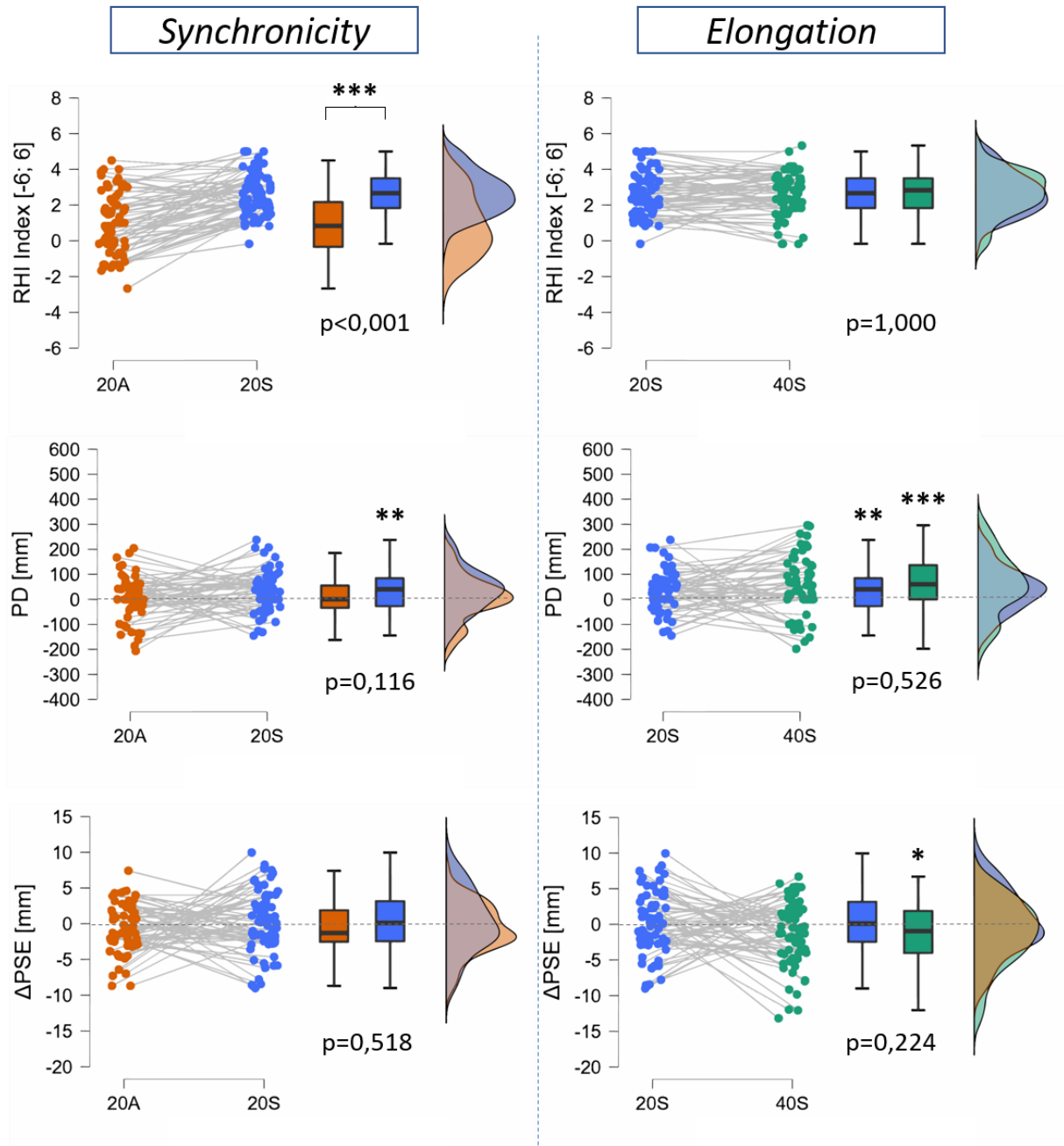


Figure 10, Raincloud plots showing results of the general analysis on the synchronicity effect (left) and elongation effect (right) on the Rubber Hand Illusion (RHI) Index (top), Proprioceptive Drift (PD) (middle) and Delta Point of Subjective Equality (Δ PSE) (bottom). Asterisks on top of a singular box plot (without brackets) indicate the significance level of the difference from 0. Asterisks on top of brackets indicate the significance level of the difference between the indicated conditions and the corresponding p-value is displayed below the box plots. Asterisks meanings: $p < 0.05$: *; $p < 0.01$: **; $p < 0.001$: *.**

1st condition analysis

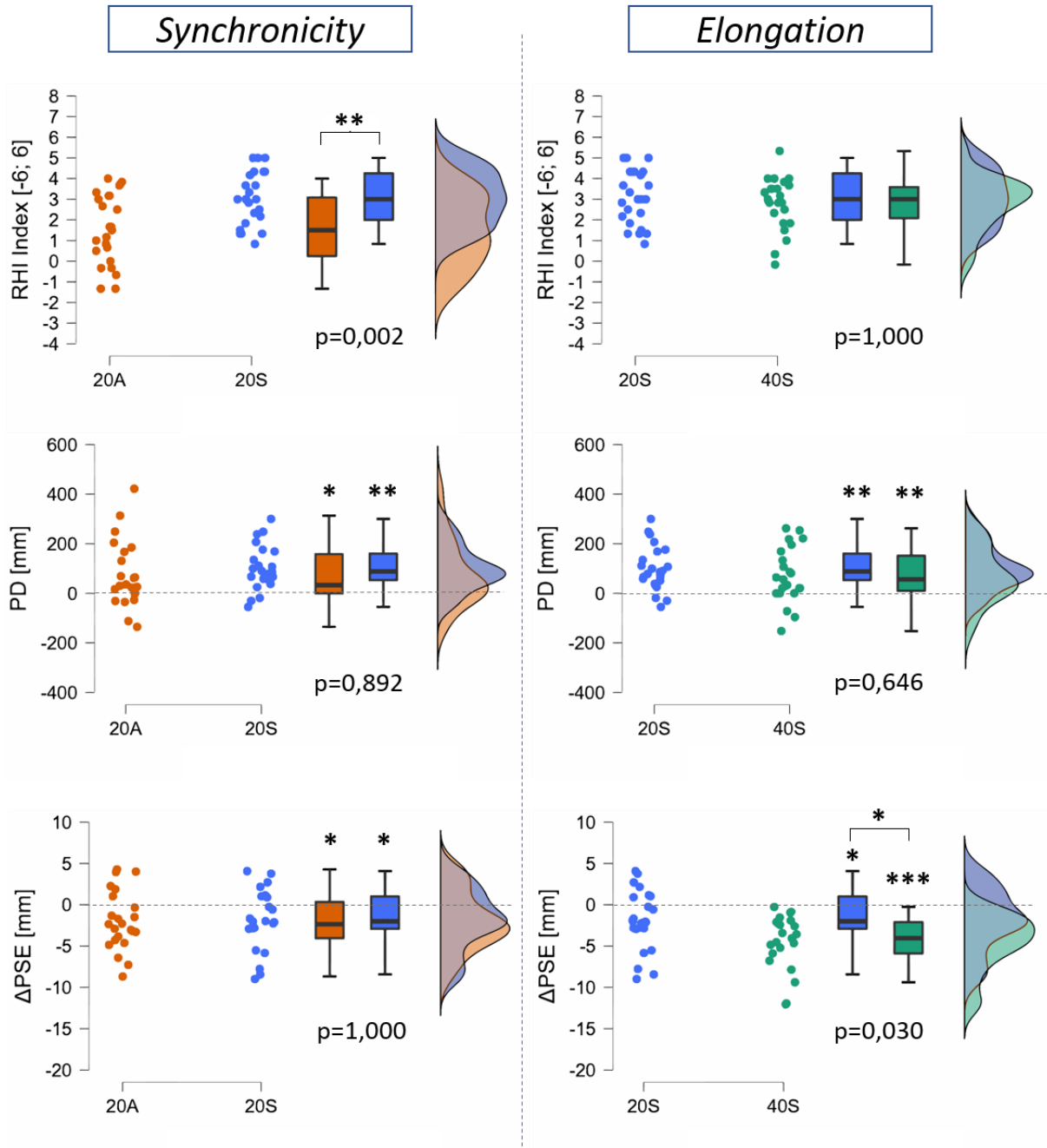
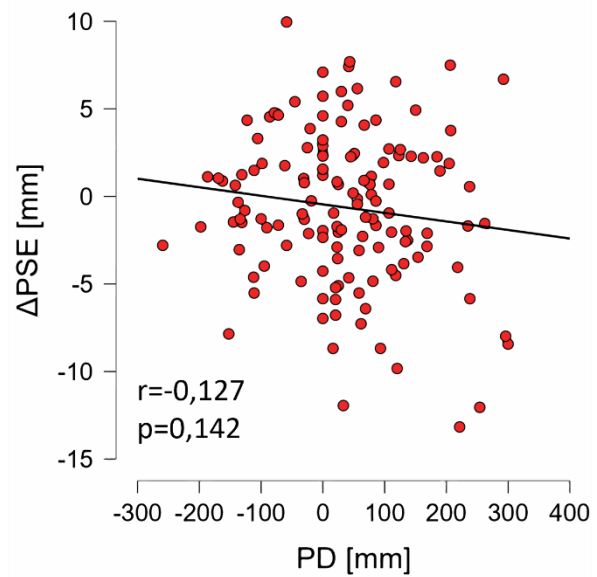
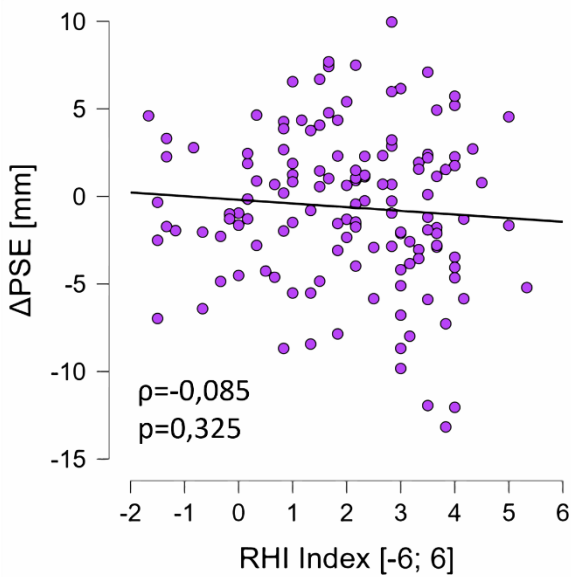


Figure 11, Raincloud plots showing results of the first condition analysis on the synchronicity effect (left) and elongation effect (right) on the Rubber Hand Illusion (RHI) Index (top), Proprioceptive Drift (PD) (middle) and Delta Point of Subjective Equality (ΔPSE) (bottom). Asterisks on top of a singular box plot (without brackets) indicate the significance level of the difference from 0. Asterisks on top of brackets indicate the significance level of the difference between the indicated conditions and the corresponding p-value is displayed below the box plots. Asterisks meanings: $p < 0.05$: *; $p < 0.01$: **; $p < 0.001$: *.**

General analysis



1st condition analysis

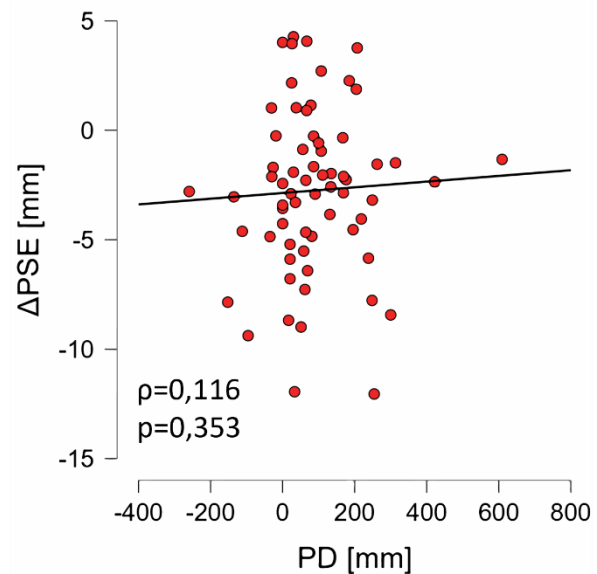
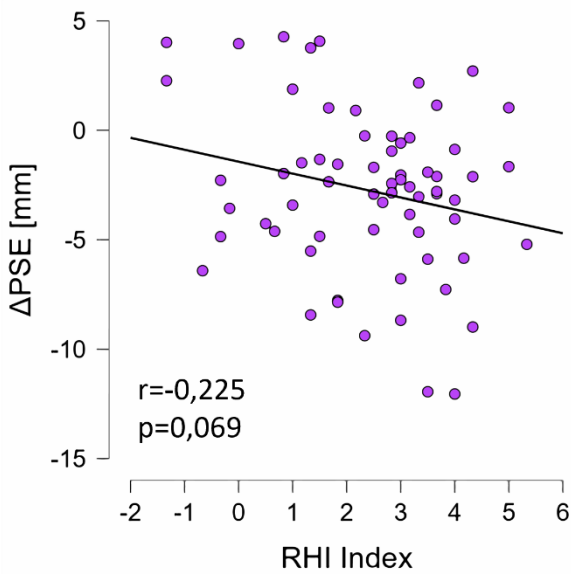


Figure 12, Correlations plots for the general analysis (top) and for the analysis on the first condition (bottom): Rubber Hand Illusion (RHI) Index and Delta Point of Subjective Equality (Δ PSE) (left), PD and Δ PSE (right). ρ and r represent Spearman's ρ and Pearson's r , respectively.

4.5 Discussion

The aim of the study was to understand whether the change in Tactile Distance Perception (TDP) following a bodily illusion demonstrated by previous studies (de Vignemont et al., 2005; Taylor-Clarke et al., 2004) could take place through *embodiment* over a fake limb. We used a Virtual Hand Illusion (VHI) paradigm with an elongated forearm in a 1PP virtual environment to induce the bodily illusion of owning an elongated forearm and assessed the resulting change in subjective perception of distance between two simultaneously touched points using a Tactile Distance Perception Task (TDPT). To test the effect of the *elongation* magnitude, we compared the data obtained by exposing participants to a synchronous VHI with the virtual forearm elongated by 40cm (40S) to the data obtained after a synchronous VHI with a shorter elongation (20cm, 20S). To assess the effect of the *synchronicity* of the VHI, the data relative to the 20cm elongation synchronous VHI (20S) were compared to the data relative to the asynchronous VHI with equal elongation (20A). We also investigated the correlation between different aspects of the elongated forearm embodiment and the changes in TDP. The embodiment illusion proved effective, as participants perceived a significantly higher level of ownership (from the Rubber Hand Illusion (RHI) Index) after the synchronous VHI compared to the asynchronous condition. Our experiment confirms previous findings on the effectiveness of synchronous visuo-tactile stimulation in eliciting ownership over a virtual limb (Pyasik, Tieri, & Pia, 2020; Slater, Perez-Marcos, Ehrsson, & Sanchez-Vives, 2008).

Furthermore, no effect of the forearm elongation on the perceived ownership was highlighted as both elongation magnitudes (under synchronous VHI) resulted to have non-significantly different RHI Index values. This comes in line with previous results showing that it is possible to embody a fake hand placed farther than the real one along the distal plane with a RHI or VHI paradigm (Armel & Ramachandran, 2003a; Kalckert, Perera, Ganesan, & Tan, 2019a; Kilteni, Normand, Sanchez-Vives, & Slater, 2012b). More specifically, previous study (Kilteni et al., 2012c) showed a steady ownership level with a virtual forearm of one, two and three times the normal forearm length. Considering that the elongation magnitudes (20 and 40 cm elongations) of our study are comprised in these lengths (forearm length of participants: $25,77 \pm 2.22$ cm, thus a times-three forearm length would be equivalent to a 50 cm elongation), our results confirm the finding of such previous study.

From the general analysis, synchronous conditions (20S and 40S) caused a significant drift of the perceived position of the hand from the one perceived prior to the VHI towards the position of the virtual hand visualized during the VHI, whereas the asynchronous condition (20A) did not. This result would hint towards an effect of the synchronicity of the VHI on the Proprioceptive Drift (PD) with a higher PD due to the synchronous VHI with respect to the asynchronous VHI. Nevertheless, VHI

synchronicity was not found to influence the PD (no significant difference in PD between 20A and 20S conditions), neither was the forearm elongation magnitude (no significant difference in PD between 20S and 40S conditions). Unconclusive results were also found considering the change in TDP. Indeed, the greater elongation condition (40S) significantly increased the TDP (significantly decreased the PSE) with respect to the pre-VHI perception, whereas smaller elongation conditions (20A and 20S) did not. This would suggest the presence of an effect of the elongation magnitude of the virtual forearm, with greater increases in TDP for greater elongations. However, the virtual forearm elongation magnitude did not prove to influence the TDP (no significant difference in Δ PSE between 20S and 40S condition), and neither did the VHI synchronicity (no significant difference in Δ PSE between 20S and 20A condition).

Different factors could have affected our results. Testing multiple repetitions of the RHI paradigm successively could have decreased participant sensitivity to the illusion. Additionally, participants underwent all conditions successively without removing the headset nor moving their left arm. Therefore, no proper “reset” of the experimental conditions took place between the different conditions, and thus the effects of one condition might have been transferred to the successive condition. These issues could have affected the second and third conditions undergone by participants but not of the first one. Therefore, the between-subjects analysis restricted to the first tested condition is free of these potential effects.

Considering the perceived embodiment of the virtual hand through the VHI, the analysis on the first condition gave identical results as the previous analysis. However, the analysis on the first condition revealed that participants perceived the position of their real hand significantly drifted towards the position of the virtual hand located at the end of the virtual forearm with respect to the normal (pre-VHI) perceived hand position after all VHI conditions, independently from the VHI *synchronicity* or the magnitude of *elongation*. The lack of influence of the *synchronicity* of stimulation on PD and the lack of correlation between the RHI Index and PD indicate a dissociation between the VHI-induced embodiment and the PD, corroborating the findings of previous findings (Rohde et al., 2011) on the absence of a relationship between RHI-paradigm-induced ownership and PD in a real environment. We could suggest that here the drift in perceived hand location is mainly caused by the visual feedback from the elongated upper limb. Moreover, in their real environment (Rohde, Di Luca, & Ernst, 2011) additionally found that long asynchronous stimulation (120s) prevented the PD. On the contrary, we found PD to be robust to asynchronous stimulation (PD significantly higher than 0 for asynchronous stimulation, and no significant difference between asynchronous and synchronous conditions). Our stimulation was slightly shorter (90s), but we did not think that such limited difference in stimulation duration (30s) could affect the outcome. We thus further suggest that the

robustness of the PD we observed is due to the strength of the visual feedback that participants receive from their avatar in the case of a 1PP immersive virtual reality, which is corroborated by the findings of Perez-Marcos and colleagues (Perez-Marcos, Sanchez-Vives, & Slater, 2012). The absence of a virtual forearm elongation effect on the PD (no significant difference between 40S and 20S) is an intriguing finding. We could hypothesise that proprioception is malleable but bounded to some extent by our natural body schema (prior to its alteration) and insensitive to excessive distortions. Indeed, (Kilteni et al., 2012c) found the PD to be significantly greater than 0 with a virtual forearm of two and three times the length the real limb length (equivalent to our 20cm and 40cm elongation respectively) but without any significant increase of the elicited PD for the times-three condition with respect to the times-two condition. They furthermore found the PD effect to be seemingly limited to a times-three forearm length by finding an absence of PD for a times-four forearm length. The analysis of the first condition on Δ PSE showed that participants perceived an increase in TDP on the real forearm after all elongated VHI conditions and that a greater virtual forearm elongation results in a greater augmentation in TDP (Δ PSE due to 40S significantly lower than Δ PSE due to 20S), thus that the magnitude of virtual forearm *elongation* matters in determining the changes of TDP. However, neither this analysis showed an effect of *synchronicity* of the VHI on the modification of the TDP. Therefore, the presence of the *elongation* effect and the absence of a significant *synchronicity* effect, combined also with the absence of correlation between RHI Index and Δ PSE suggest that in our study the modification of the TDP might be dissociated from the embodiment of the virtual hand elicited by the VHI paradigm. In line with the change in TDP caused by the visual modification of body proportions performed previously (Taylor-Clarke et al., 2004), we suggest that here the modulation of TDP by the virtual forearm elongation magnitude is mainly induced by the changes in the *visual* experience of the virtual body. Thus, the visual feedback here plays the main role in the modification of the body schema. This is also partly in line with what was found by other authors (Linkenauger, Leyrer, Bühlhoff, & Mohler, 2013) where a change in the visually perceived sizes of objects was found after participants experienced, in 1PP VR, vision and agency over a virtual hand of modified dimensions but without any form of visuo-tactile stimulation. On the other hand, similar studies performed *in real environments* did find correlations between the changes in visual (van der Hoort, Guterstam, & Ehrsson, 2011) or proprioceptive (Bruno & Bertamini, 2010) perception of objects dimensions and the perceived embodiment, induced by a RHI paradigm, of a full-body or a rubber hand (respectively) of dimensions bigger or smaller than normal. They thus proved the existence of a link between a bodily illusion induced by the embodiment of a foreign body part and the modification of perception. Additionally, considering that embodiment of a virtual body can be elicited solely by vision in the case of an immersive 1PP virtual experience (Bourdin, Martini, &

Sanchez-Vives, 2019; Maselli & Slater, 2013; Pavone et al., 2016; Spinelli, Tieri, Pavone, & Aglioti, 2018), it can be hypothesised that the modification of TDP observed in our study might still be linked to an embodiment phenomenon towards the virtual body, known in literature as *virtual embodiment* (Argelaguet, Hoyet, Trico, & Lecuyer, 2016; Bailey, Bailenson, & Casasanto, 2016; Matamala-Gomez et al., 2019).

This might have overridden the visuo-tactile stimulation of the VHI paradigm as the main cause for embodiment. Considering that the RHI Index extracted from the questionnaire overfocuses on visuo-tactile integration and does not consider the virtual embodiment, we can hypothesise that the visuo-tactile stimulation synchronicity might induce a level of embodiment too low (with respect to the virtual embodiment) to find a correlation between the modification of TDP and the RHI index in our study. Finally, whereas the TDP and the PD reveal modifications of body schema (de Vignemont, 2010, 2011; Romano, Caffa, Hernandez-Arieta, Brugger, & Maravita, 2015; Segura Meraz, Sobajima, Aoyama, & Hasegawa, 2018), here the presence of a significant effect of the *elongation* magnitude of the virtual forearm on the variation of the TDP in the absence of its influence on PD, coupled to the lack of correlation between Δ PSE and PD, suggests that the TDP (assessing tactile exteroceptive information) and the PD (assessing the proprioceptive information) are dissociated and affected differently by changes of the perceived dimensions of a limb, i.e., of the body schema.

4.6 Conclusions

In our everyday life, we interact with the environment using our body to sense. Like any sensor, our perception requires specific reference frames to measure parameters accurately. For instance, to perceive tactile distances we rescale our perception based on the currently perceived dimensions of the touched body part. It is believed that rescaling process involves the implicit model of the metric properties of our body constructed by the brain (the body schema). Several studies have proven the latter by modifying the body schema of participants through *own* body size modification illusions and observing a correlated modification of the TDP. In this study, we investigated the effects on TDP of a virtual elongated forearm experienced in 1PP virtual environment. Even though we found an increase of the TDP positively associated with the virtual forearm *elongation* magnitude, no link has been found between the perceived embodiment over the virtually elongated arm resulting from the visuo-tactile synchronicity of the VHI and the perceived augmentation of the TDP, suggesting that the alteration of the body schema has taken place mainly through visual feedback over the elongated body part. We further hypothesised that a virtual embodiment due to the immersive 1PP experience of a virtual body might have taken place, dominating the VHI-induced embodiment. Finally, TDP

revealed a modification of the body schema that the PD did not detect, suggesting that tactile exteroception and proprioception are affected differently by body schema modifications.

5 Neurophysiological models of phantom limb pain: what can be learnt

5.1 Critical review of the literature

Background

60% to 80% (Ugorji et al., 2019) of subjects that suffered limb amputation have often their quality of life worsened by phantom limb pain (PLP) (Sinha & Van Den Heuvel, 2011). Phantom sensation or awareness is the non-painful feeling that the lost limb is still present and kinaesthetically perceived, whereas PLP is a dysesthetic and painful sensations perceived in the lost limb. Phantom limbs can be experienced in the form of kinetic sensations (perception of movement), proprioceptive components (size, shape, position) and exteroceptive perceptions (touch, pressure, temperature, itch, vibration) (Weinstein, 1998). The phantom can be perceived as having a normal limb size, or shorter than the original limb (telescoping) with hands, fingers, or toes perceived at the level of the stump (Pirowska et al., 2014).

The majority of amputees experience PLP as burning (13.6%), cramps (15.3%), prickling (23.4%), electrification (21%) and tingling (20.4%) (Ugorji et al., 2019). In 35% of cases, PLP is associated with the reason of amputation or with stump pain originating after amputation (Kern, Busch, Rockland, Kohl, & Birklein, 2009).

Treatments

PLP pharmacological management employs CNS-acting drugs and local anaesthetics. Antidepressants, especially amitriptyline, are first-line therapies (Kaur & Guan, 2018). Gabapentin is safer than other anticonvulsants (Dworkin et al., 2010), but its efficacy for PLP is low (Fang, Lian, Xie, & Cai, 2013). Strong Opioids are effective (Wu et al., 2008; Wu et al., 2002), while tramadol – a weak opioid μ -receptor agonist – is rapid but less effective (Fang et al., 2013). Memantine, an NMDA glutamate receptor antagonist, is effective in acute pain (Hackworth, Tokarz, Fowler, Wallace, & Stedje-Larsen, 2008), yet less effective on chronic one (Maier et al., 2003; Wiech et al., 2004). Local anaesthetics, (e.g. lidocaine – a sodium channel blocker) injected into the dorsal root ganglion transiently relieve PLP (Vaso et al., 2014).

Interestingly, there are no proofs that combination of medications is superior to single drug (Fang et al., 2013). Other treatments include mirror and cognitive behavioral therapy, neuromodulation, and

surgery (Modest, Raducha, Testa, & Ebersson, 2020). Also transcutaneous electrical nerve stimulation (TENS) has been proved to be helpful (Black, Persons, & Jamieson, 2009; Katz & Melzack, 1991). Despite such wide choice of possible treatments, PLP remains often not completely resolved, and sufferers exhibit high psychological and emotional distress (Katz, 1993), anxiety and mood disturbance (Fuchs, Flor, & Bekrater-Bodmann, 2018).

Models of Phantom Limb Pain

The origin of PLP has intrigued scientists for long (Finger & Hustwit, 2003; Nathanson, 1988). Initially, PLP was believed to have no organic roots and its psychological consequence were misinterpreted as its cause (Weinstein, 1998). Today, PLP is believed to be the result of complex interactions between structural and functional changes of the central and peripheral nervous systems. Here we analyse the main pathogenetic models of PLP (Figure 13) and speculate on candidate therapeutic targets. Here, we consider a “model” as a theoretical abstraction useful to circumscribe the object of investigation and examine the variables at play.

Peripheral pathogenesis behind PLP was popular in the past and had recently regaining relevance. The *neuroma model* considers PLP to arise from the spontaneous activity of ectopic hyperexcitable loci on injured axons within the residual limb (Collins et al., 2018). Although the brain might misinterpret impulses generated at the residual limb as originating from the absent limb (Finnoff, 2001), it may be more appropriate to refer to such pain as “neuroma pain” (Ortiz-Catalan, 2018). Whereas neuromas can result in pain perceived in the missing limb treatable by surgical interventions (Dumanian et al., 2019; Woo et al., 2016), maladaptive changes in the central nervous system can maintain PLP without a neuroma. Moreover, stump pain should be resolved as it can be a trigger of PLP.

Other models on the peripheral origin of PLP hypothesise that damaged residual somatosensory receptors may produce unwanted discharge causing allodynia (Campbell et al., 1989), or that non-neural factors, such as vascular changes in the stump, may contribute to phantom pain (Sherman & Bruno, 1987).

Alongside peripheral models, others focus on central mechanisms. After injury and loss of bidirectional nervous flow, a topographical and functional reorganisation of the nervous system takes place, pushed by the need to enhance alternative functions vicariate for the hand loss, (Di Pino et al., 2009). An initial unmasking of existing but functionally-silent synaptic connections due to the lack of “surround” inhibition from the “orphan” area is followed by a later arising of new path connecting the areas controlling the lost limb with adjacent regions (Jones, 2000). Such cortical reorganisation

sets the stage for the *cortical remapping model*, which is one of the most popular explanations for the PLP.

Afferents from skin in the upper arm and face “invade” the hand territory, in line with the hand cortical representation setting, which is in between the face area on one side and the upper arm on the other (Ramachandran & Rogers-Ramachandran, 2000).

Built upon an older hypothesis (Katz, 1992), a keystone study shifted the focus to the CNS by showing that the amount of somatosensory cortical reorganisation correlates with the magnitude of PLP, not with non-painful phantom phenomena (Flor et al., 1995), suggesting PLP as directly correlated with plastic changes occurring in this cortex. Along this line, PLP patients showed a shift of the lip representation toward the deafferented primary motor and somatosensory hand areas (Lotze, Flor, Grodd, Larbig, & Birbaumer, 2001).

The *remapping model* could explain telescoping; since the cortical representation of the hand is wider and “stronger” compared to that of the forearm, and thus transradial amputations are less likely to develop a phantom forearm (Rossini et al., 2010; Schmalzl & Ehrsson, 2011).

However, recent experiments found no clear correlation between cortical reorganisation and PLP challenging the orthodoxy of this relationship. In the *persistent representation model*, maintained representation and continued inputs are supposed to preserve local structures and their functions in an experience-dependent manner (Makin & Flor, 2020; Makin et al., 2013). Instead to a shrinkage of the lost limb representation, this model associates greater PLP with stronger cortical activity and larger representation of the phantom. In support of this model, it was found that the amount of PLP reduction experienced by patients undergoing transcranial direct current stimulation, while producing phantom motor execution, inversely correlates with the level of activity in the affected sensorimotor areas (Kikkert et al., 2019). Prior studies have found a reduction of PLP by transcranial direct current stimulation alone (Bolognini et al., 2013), but the combination with phantom motor execution has been theorized as more effective in other models (Ortiz-Catalan, 2018). In addition, similar cortical activity has been observed between able-bodied and subjects with amputations, but latter showed a disruption of inter-regional functional connectivity between homologous cortices governing the intact and the lost limb, which reflects a repeated lack of their co-activation (Makin et al., 2013).

Looking at the topic from a different perspective, the concept of body image and schema, the brain dynamic representation of the spatial and biomechanical properties of one’s body, derived from sensory inputs and from the copy of the motor commands during the interaction with the external world (Pinaridi, 2020), could provide a template for understanding phantom limb syndrome after interruption of sensory feedback (Di Pino, Maravita, Zollo, Guglielmelli, & Di Lazzaro, 2014; Giummarra, Gibson, Georgiou-Karistianis, & Bradshaw, 2007b).

During an anaesthetic block of the brachial plexus, patients report their limb to be in one or two predominant postures, which do not vary among patients and ignore the actual position of the limb, as if the posture was coded in a static physical-self (Melzack & Bromage, 1973). This possibility disrupts the traditional view of the body representation as being only a continuously updating projection of sensory feedback. Melzack hypothesises that this representation relies on a genetically determined network connecting the cortex with the thalamus and the limbic system, named *neuromatrix* (Melzack, 1990, 2001).

Neuromatrix is the base for a further PLP model suggesting that subject's body representation remains intact despite limb amputation, but it no longer matches the real body appearance. This mismatch generates pain without nociception and is responsible for PLP.

Accordingly with a static representation hypothesis, both the quality and location of the phantom pain are the same of the pre-amputation pain in 60% of subjects who reported pain around the time of amputation (Katz & Melzack, 1990).

However, the predictive value of pre-operative pain for post-amputation pain has been debated (Weinstein, 1998) and recent studies found no correlation between pre-amputation pain and PLP (Richardson, Crawford, Milnes, Bouch, & Kulkarni, 2015).

Nonetheless, memory seems to play a crucial role in the perception of PLP. It has been suggested that pain is encoded prior to the amputation and can later be triggered by external stimuli (Katz & Melzack, 1990), and that phantom sensations are effect of *proprioceptive memories* which associated specific limb positions with the pain felt before the amputation (Anderson-Barnes, McAuliffe, Swanberg, & Tsao, 2009a). Following the amputation, memories of motor and sensory information for a limb may be recalled (Weeks, Anderson-Barnes, & Tsao, 2010), as when during regional anaesthesia patients refer to perceive limb position different from the actual one (Bromage & Melzack, 1974b; Gentili, Verton, Kinirons, & Bonnet, 2002). Visuo-proprioceptive incongruence is due to proprioceptive memories of the lost limb and visual awareness that the limb is missing.

Finally, the *stochastic entanglement model* is a recent attempt to explain PLP (Ortiz-Catalan, 2018). Previous ideas on the genesis of PLP lack of a direct relationship between observed phenomena (e.g., cortical reorganisation) and the neural circuitry generating the experience of pain. Amputation drastically disrupts cortical, sub-cortical, and spinal motor and somatosensory circuits, potentially allowing for maladaptive wiring with pain processing circuits. If under ordinary circumstances pain perception network are solely activated because of noxious stimuli, a stochastic entanglement between sensorimotor and pain networks following deafferentation could cause pain without nociception.

However, existing – and apparently contradicting – theories might not be mutually exclusive: the remapping and persistent representation models could coexist in a scenario in which a partial cortical reorganisation occurs while a part of the limb representation is still preserved, or in case of overlapping (Raffin, Richard, Giraux, & Reilly, 2016). The persistent representation model shares with Melzack's hypothesis the idea that PLP arises while the representation of the limb remains mostly unchanged.

Another explanation which holds for several models sees maladaptive plasticity not mainly affecting the extension of the cortical representation or its absolute activity, but other functional features, such as the interplay with relevant areas. Peripheral factors such as neuromas and vascular changes might not directly maintain PLP but, they could contribute to the stump pain that, in turn, could exacerbate PLP driving it to chronicity.

One holistic approach to the complexity of the phenomenon was already suggested in the late nineties, where at least five different causes were argued to play a role in PLP: stump neuromas, cortical remapping, monitoring of corollary discharge from motor commands to the limb, one's body image and vivid somatic memories of painful sensations or posture of the original limb translated into the phantom (Ramachandran & Hirstein, 1998a). These components were thought to work together and influence each other; as a result, subjective experience of PLP may vary substantially from one patient to another. However, the necessity of each of these components, and the exclusion of others, remains an open question.

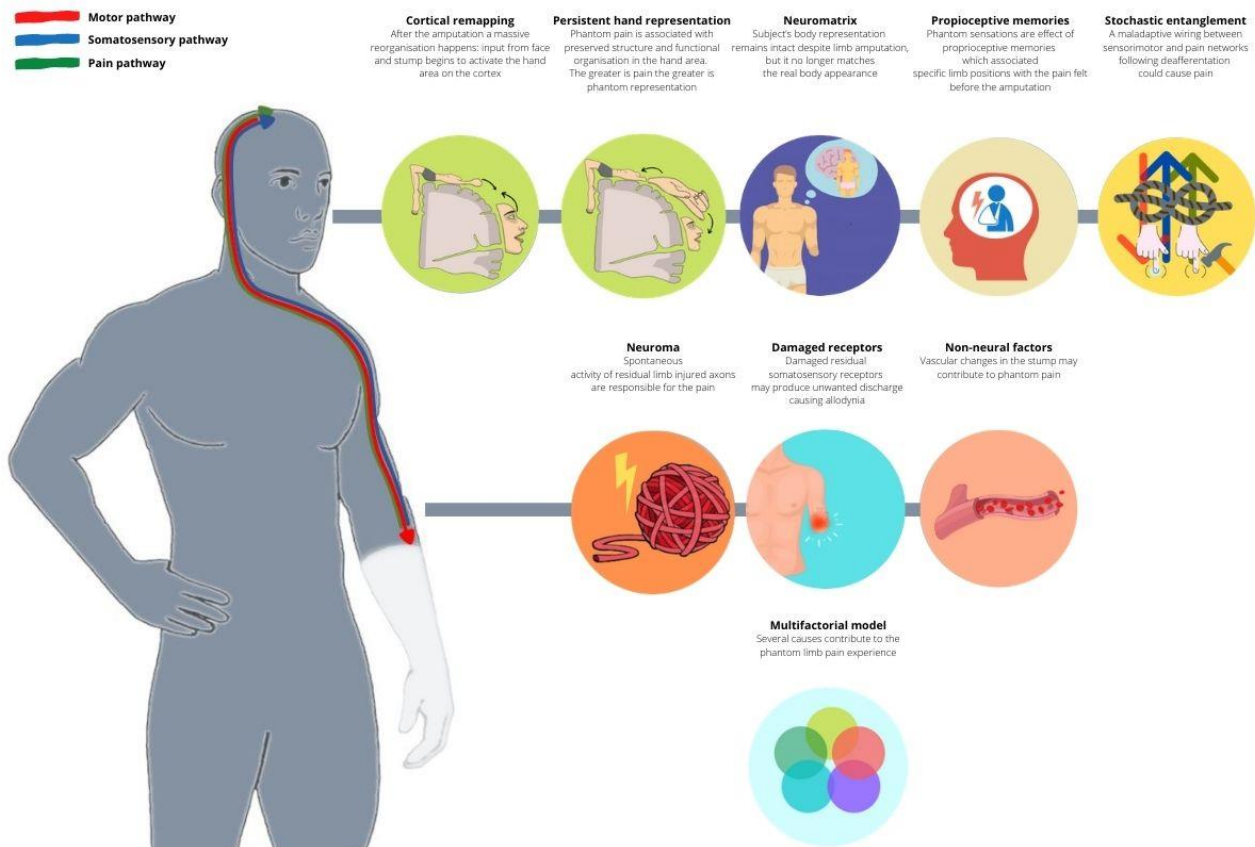


Figure 13, Brief graphical description of phantom limb models.

Discussion & conclusion

All considering, it emerges clearly that together with the pharmacological management of pain, the complex nature of the phenomenon is better faced by a multilevel care approach designed to achieve physical and psychological recovery.

From this brief overview of the neuropathogenetic hypotheses behind PLP, few suggestions can be gathered. PLP complexity and its tight relation with other types of pain (e.g. stump or dysautonomic pain) can easily lead to a PLP wrong diagnosis. Improving our knowledge of the phenomenon is the first step towards the most accurate therapeutic approach.

For instance, it is interesting to note how using a prosthesis can modulate body-related sensorimotor integration (Di Pino et al., 2020b), which is the basis on which the representation of the body is built, and it can also reduce the perceived pain (Horch, Meek, Taylor, & Hutchinson, 2011; Ortiz-Catalan, Håkansson, & Brånemark, 2014; Ortiz-Catalan, Mastinu, Sassu, Aszmann, & Brånemark, 2020; Rossini et al., 2010; Tan et al., 2014). Interestingly, the use of prostheses was reported to normalise intra and interhemispheric functional activity and connectivity (Di Pino et al., 2012; Ferreri et al., 2014), and it was negatively correlated with cortical reorganisation and positively correlated with the reduction of PLP (Lotze et al., 1999).

There are several intertwined potential mechanisms by which replacing an amputated limb by an artificial one would counteract PLP, such as 1) re-engaging of motor and somatosensory neural circuitry, 2) normalising sensory inputs and motor outputs, 3) normalising primary sensorimotor cortical representation, 4) normalising body representation in the frontoparietal network, 4) resolving conflicts among sensory modalities or with the motor commands, and 5) embodying the prosthesis into the body representation (Di Pino et al., 2020b).

The *stochastic entangle* model stipulates that relief of PLP depends solely on the engagement of motor and somatosensory circuitry, making anthropomorphic visual feedback desirable but dispensable (Ortiz-Catalan, 2018). In this case, PLP would also be eliminated with a prosthesis that looks nothing like a human limb, so long its control relies on the missing limb's motor and somatosensory neural circuitry. This is in sharp contrast with the most popular views of models relying on the resolution of sensory-motor incongruence and restoration of body representations, where anthropomorphic visual feedback is not only highly valued but necessary. It is worthy of notice that visual feedback alone is not enough, as a realistic, anthropomorphic, but passive prosthesis does not resolve PLP, while therapies without anthropomorphic visual feedback have shown to relieve PLP (Bolognini et al., 2015; Brodie, Whyte, & Niven, 2007; Kikkert et al., 2019; Ortiz-Catalan, 2018).

The utility of a model relies on its ability to accurately predict empirical data, while avoiding unnecessary complexity. We are still far from grasping a full understanding of the PLP phenomenon, for instance, there is contradicting reports on congenital and acquired deafferentations (Flor et al., 1998; Melzack, Israel, Lacroix, & Schultz, 1997; Ramachandran, 1993), which PLP models should be challenge with. Providing testable hypothesis and explicitly stating the expected prediction, while also increasing collaboration between researchers in the field, would help further understanding of the phenomena.

6 Visual feedback in modulation of pain perception: neurophysiological perspective on a virtual reality Phantom Limb Pain modelling

6.1 Introduction

In the previous chapter we extensively discussed the importance of a multifactorial approach to the understanding of the phenomenon of phantom limb pain. However, precisely because of this complexity, every potential cause deserves thorough investigation and should be integrated into a broader perspective afterward. Here, with the aim of exploring the contribution of body image to phantom limb pain, the main objective of our investigation is examining the impact of missing or altered visual feedback on pain modulation. Normally, the frontal lobe sends instructions for voluntary movement to the muscles. These instructions are monitored by the parietal lobes, which simultaneously receive feedback from the limb regarding its position, posture, and movement. In this simplified manner, the brain maintains a certain coherence between the actual configuration of the body and its representation. But what happens if the arm or a part of it is missing? Some authors suggest that messages coming from the motor cortex continue to be sent to the muscles despite the absence of the limb or part of it (Ramachandran & Rogers-Ramachandran, 1996). While in able-bodied subjects the execution of movements is verified through visual and proprioceptive feedback from the healthy limb, in amputees the absence of such feedback creates a conflict that appears to play a role in pain. In support of this theory, mirror therapy, where a mirror is placed parasagittally between the patient's arms so that the mirror reflection of the patient's intact arm or hand is overlapped on the felt position of the phantom, can induce pain relief (Ramachandran & Rogers-Ramachandran, 1996). Reflecting an image of the intact hand via a mirror is thought to reestablish the coherence with the missing hand's representation within the primary somatosensory cortex (Makin, 2021). Such neuroplasticity phenomena also underlie the graded motor imagery, a related method which uses mental visualisation exercises (Moseley, 2006). However, mirror therapy is more effective than motor imagery (Chan et al., 2007) suggesting a pivotal role of the visual feedback in modulating body representation and, in turn, pain. Similar results come from the use of augmented reality, which can improve pain and reduce the consumption of medications (Ortiz-Catalan et al., 2016).

Experimentally, visual feedback has been manipulated in several ways to investigate its effect on pain. Curiously, despite the urgent and primitive quality of pain, its localisation can be disrupted by

misleading visual signals, and visual capture may dominate the interplay between vision, proprioception, and the pain itself (Capelari, Uribe, & Brasil-Neto, 2009). In this context, self-related modulation assumes particular importance: visual feedback modulation, indeed, induces analgesia only by viewing at one's own body but not at stranger's body (Longo, V., Aglioti, & Haggard, 2009) or a non-body object (Romano, Pfeiffer, Maravita, & Blanke, 2014). This analgesic effect seems to be also related to the scaling of the body part subjects are viewing. For instance, if the hand appears larger than in reality, the pain-relieving effect of seeing the hand is enhanced; conversely, if the hand appears smaller such effect is reduced (Mancini et al., 2011). Interestingly, these results contrast with a previous study on chronic pain, where enlarging the limb increased experienced pain (Moseley, Parsons, & Spence, 2008). However, the characteristics of studied subjects suggest that differences in results may be due to distinct neurophysiological mechanisms underlying acute and chronic pain. Shape also appears to have a significant impact on pain: using the RHI, some researchers have demonstrated the influence of a negative body image (rubber injured arm) on the perceived discomfort and a consequent increase in pain, emphasising that the analgesic effect of viewing one's own arm is only possible in the absence of negative perceptual experiences associated with pain (Osumi, Imai, Ueta, Nobusako, & Morioka, 2014). Similarly, in a VR environment, the colour red on the arm, likely associated with the effect of a burn, decreases pain thresholds, while the colour blue increases them (Martini, Pérez Marcos, & Sanchez-Vives, 2013). If the transparency of the limb in VR environment is modulated, it has no direct impact on pain thresholds but it reduces the illusion of ownership (Martini et al., 2015). Moreover, when higher levels of ownership over a transparent body were experienced, they resulted in an increased pain sensitivity. The opposite effect on pain threshold occurs when the body is represented with its normal features (no transparency or colour modulation). Here, the ownership of the avatar's limb can significantly increase the thermal pain threshold in that limb (Martini, Perez-Marcos, & Sanchez-Vives, 2014). Confirming previous findings on the effect of ownership on analgesia, other studies report that self-identification with a virtual body can reduce implicit arousal responses (SCRs) to acute painful stimuli (Romano et al., 2014) and that both normal and larger virtual bodies induced more significant reductions in physiological responses compared to a smaller virtual body (Romano, Llobera, & Blanke, 2016). However, these manipulations did not impact participants' subjective pain ratings, suggesting that SCRs and pain ratings were assessing distinct facets of pain processing. Compelling results come from a recent study in which the effect of telescoping in VR was examined using a threatening paradigm (Matamala-Gomez, Nierula, Donegan, Slater, & Sanchez-Vives, 2020). It was observed that there was an increase in SCRs and discomfort associated with pain when comparing the telescoping condition with the normal virtual arm condition. However, there was a reduction in SCRs when, in addition to telescoping, the arm also exhibited a

reddening effect. In line with previous findings (Romano & Maravita, 2014), the authors suggested the role of anticipatory pain response which resulted in reduced SCRs following the threatening stimulus.

In view of all this, with the aim of creating a model of PLP, we investigate the impact of virtually altered body images (arm length, hand visibility and presence of the injury) on subjective pain and autonomic responses. We expect that visual feedback may have modulate subjective ratings and autonomic responses, and we hypothesise that conditions deviating further from normality will have a greater impact on pain processing.

6.2 Materials and methods

Participants

10 right-handed participants (5 males, 5 females; mean age: 31.9; SD: 7.23) were enrolled in the pilot experiment and 28 right-handed participants (16 males, 12 females; mean age: 25.7; SD: 5.8) in the principal experiment. Data from 10 subjects were excluded from the principal experiment because they were non-responders to electrodermal activity (EDA). The study was approved by the local Ethics Committee (EMBODY protocol). All participants signed a written informed consent made in accordance with the Declaration of Helsinki and later amendments.

Setup

Participant sat comfortably on a chair in front of a table placed within a 2.40m x 2.00m x 1.80m metallic structure. Both in the pilot and in the principal experiment they were stimulated with a peripheral neuropathy screening device (Neuropen®, Owen Mumford) accessorised with a single use neurological examination tip (Neurotips®). The device is designed to deliver constant 40g intensity pinprick pain. To obtain epochs for the recording of the electrodermal responses evoked by the pinprick pain, the device was connected to a Power1401 A/D converter (Cambridge Electronic Design Limited, Uk). When the pain stimulation was delivered with a 40g pressure, a custom-made circuit was closed, allowing a current to pass from the DAC to an ADC port. Signal 5.08 software (Cambridge Electronic Design Limited, Cambridge, Uk) was employed to synchronise the ADC signal with a Power1401 digital output to be sent to the EDA recording device (Biopac MP160). The EDA was recorded at DC level. Biopac acquisition sample rate was 2kHz. Two electrodes were applied to the distal phalanges of the index and the middle finger (Scerbo, Freedman, Raine, Dawson, &

Venables, 1992) of the subject's left hand to acquire the EDA signal. This was visualised on a screen via the *AcqKnowledge*® Acquisition and Analysis software (Biopac).

In the principal experiment, participants visualised the immersive virtual environment through a virtual reality (VR) system (HTC Vive, HTC Corporation). They wore a VR headset (head mounted device – HMD) and the HMD movement was tracked by two infrared cameras (base-stations). To allow the immersion of participants inside the virtual environment and their sense of agency over the virtual avatar, the movements of their real arms and forearms, were tracked by motion capture systems. Left and right arm and forearm movements were tracked with four infra-red cameras (Optitrack 13W, Natural Point, Inc) and reflective optical markers worn by the participant, whereas right hand movements were tracked by a sensorised glove (CyberGlove II, CyberGlove System LLC). We developed a VR environment (using the game engine Unity, version 2018.3.0, Unity Technologies) which replicates the lab room where the experiment was run, including the table and the chair. In the virtual environment, participants saw in a first-person perspective (1PP) their avatar's body sitting in front of the virtual table. The virtual avatars were created with the open-source software MakeHuman™. Seven different VR scenarios (Figure 15) were displayed to the participants: *no feedback*, the room, table and chair were visible as in any other scenario, but there was no avatar; *normal*, the subject saw an avatar with a typical body; *injury*, the subject saw an avatar with a typical body but with a lesion on the wrist; *telescoping*, the subject saw an avatar with the left arm shortened; *trans-radial*, the subject saw an avatar with the left arm amputated at the trans-radial level and a lesion on its extremity; *trans-humeral*, the subject saw an avatar like the previous one but with a trans-humeral level of amputation; *blurring*, the subject saw an avatar with a typical body, but the vision of it was blurred by a pixelation effect.

Experimental protocol – pilot experiment

Prior to conducting the main experiment, with the aim of verifying that the device could evoke pain and that this pain was perceived by the subjects as distinct from touch, a pilot experiment was conducted. Used measures were both subjective pain ratings on a numerical rating scale (NRS) from the participants and their skin conductance responses (SCRs).

After seating the participants and connecting the EDA electrodes to their left hand, the stimulation commenced. The left hand was chosen for stimulation because pain thresholds are lower on the left side (Sarlani, Farooq, & Greenspan, 2003). Participants had their eyes closed, and the experimenter alternately stimulated the subject's back of the hand with painful stimuli (pinprick device without a needle cover) and non-painful stimuli (pinprick device with a needle cover). The hand was stimulated on an area of around 4x4 cm in a random fashion, ensuring that the same point was not stimulated

consecutively. Each stimulation block consisted of 5 trials, with a total of 3 blocks for each condition (touch, pain). The interstimulus timing was randomised to minimise the effect of expectation or habituation and simultaneously ensuring that the EDA signal could respond to each pain event (SCR) and return to its baseline after each of them. At the end of each block, participants were asked to rate the pain on a numerical rating scale (NRS) from 0 to 10, where 0 represented the perception of touch and 10 indicated the highest possible level of pain.

Experimental protocol – principal experiment

After having participants wear the markers, glove, and EDA electrodes, the experiment started with a baseline phase, during which pinprick pain was administered to subjects by using the sensorised device in three separate blocks, each consisting of 5 stimuli (Figure 15). At the end of each block, subjects were asked to evaluate the pain on a NRS ranging from 0 to 100 (“*How much pain do you feel from 0 to 100?*”), where 0 represented the perception of a touch, and 100 denoted the highest possible level of pain. This was intended to verify that the participants perceived the pain. Following the baseline phase, participants were instructed to wear a virtual reality headset and underwent a 20-second familiarisation period with all the VR conditions they would be exposed to. Participants had the ability to move both arms and perform fine finger movements with their right hand. In each of the conditions, the left arm could have varying degrees of articulation. To minimise the potential impact on agency, it was decided to restrict left-arm movements to those that could be equally performed in all conditions, including elbow flexion-extension, shoulder adduction-abduction, shoulder and arm internal-external rotation, and forearm pronation-supination. To emphasise the embodiment of the avatar, in addition to replicating the same movements with the right arm, subjects could also make fine movements of the wrist, hand, and fingers of the right hand in all conditions. During this phase, participants were instructed to attentively observe the image of their left limb.

After the familiarisation phase, the immersion phase followed, during which subjects were exposed to one of the experimental conditions for 40 seconds and they were allowed to move only the right arm, forearm, and hand.

At the end of each immersion phase, participants were asked to provide a vividness rating ranging from 0 (minimum of vividness) to 100 (maximum of vividness) (“*How vivid was the feeling that the avatar’s body was yours?*”), as well as a discomfort/unpleasantness rating on a numerical scale from 0 (minimum of unpleasantness) to 100 (maximum of unpleasantness) for the presented image (“*How much discomfort did you feel with this image?*”). As in the pilot experiment, in the stimulation phase the pinprick pain was administered to an area on the back of the hand measuring approximately 4x4 cm in a random fashion while the participants were observing a red dot (fixation point) positioned on

the furthest part of the present arm to maintain attentive focus on the altered body part. The stimulations were separated by at least 15 seconds, up to a maximum of 20 seconds. Every 5 trials, participants were prompted to rate the perceived pain on a numerical scale (0-100) as they did in the baseline phase. At the conclusion of the stimulation phase, both the immersion and stimulation phases, along with their respective subjective evaluation scales, were carried out for each experimental condition in a random order. The experiment had a total duration of approximately 1 hour and 45 minutes.

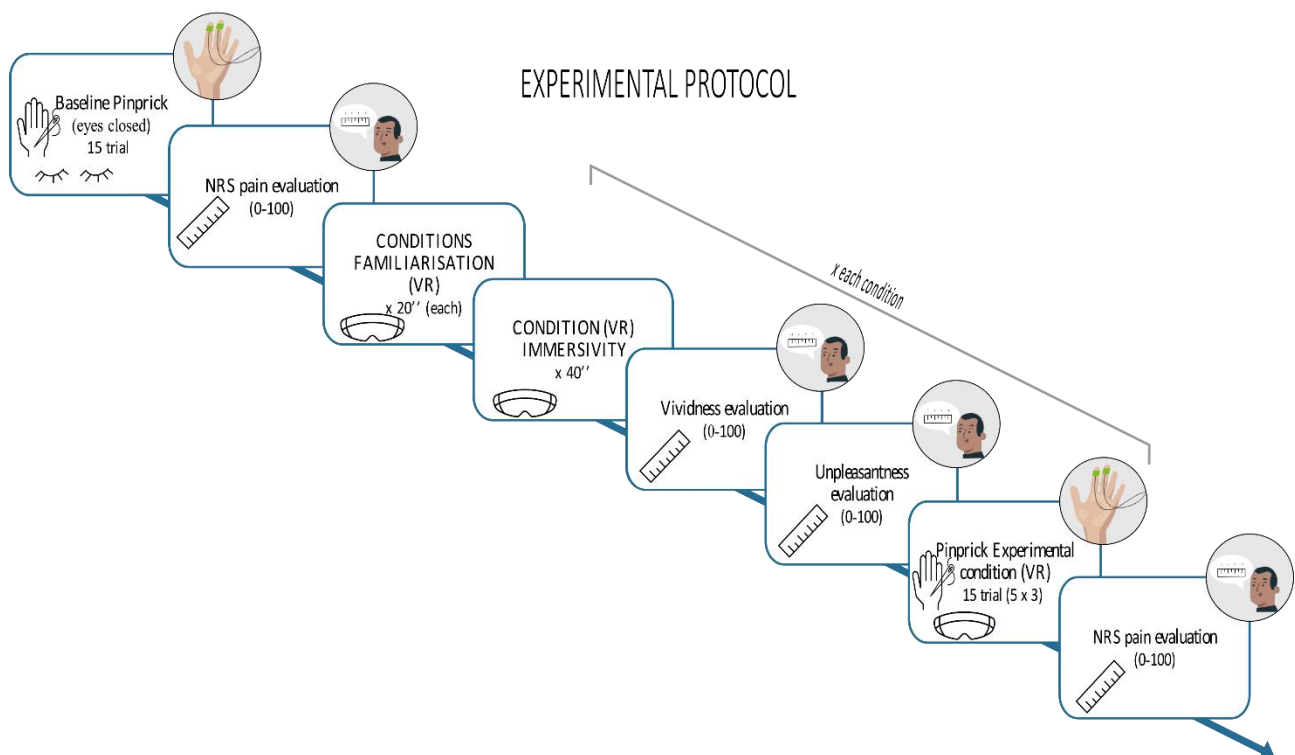


Figure 14, Graphical representation of the main experimental protocol. The boxes represent phases of the experiment and the circles the subjective and objective pain measures used.

6.3 Analysis

Pilot experiment

In the pilot experiment, the pain perceived by the subjects was assessed using a 0 to 10 NRS. EDA signal was analysed off-line using Matlab software. The raw signal was pre-processed using Butterworth bandpass filter at 0.1_10 Hz (non-phase shift, 6 dB cutoff at 0.05 and 10 Hz). Signal was then segmented on basis of the trigger event. A 1-s pre stimulus baseline correction was applied to the epoched signal. Skin conductance peak was identified on an interval of 14 seconds post trigger

using findpeak function, only the peak above 3 standard deviation 1-s pre stimulus baseline was selected. The peak identified by the function was checked by visual inspection. Peak amplitude and latency of the peak were collected.

Inferential statistics was performed with the statistical software Jasp (0.16.1.0). Since the variance in touch NRS values was 0 (all trials were rated 0), a One-sample t-test against 0 was run for pain NRS values. To investigate differences between the touch and the pain in SCRs condition a Student's paired t-tests was used. For correlation analysis, Pearson's r was calculated between SCRs expressed as a ratio of pain over touch (SCRs to pain/SCRs to touch) and NRS pain responses.

Principal experiment

For ethical considerations, the evoked pain was mild (NRS mean 26.16 ± 18.17), and after measuring it in the pilot experiment, it was decided to employ a range from 0 to 100 for the main experiment to ensure a higher resolution of the scale. Values obtained in each condition were normalised by calculating the change compared to the no feedback condition intra-subjectively. In other words, the difference between the pain NRS value obtained in each condition and the one in the no feedback condition ($nNRS = NRS\ value_{condition}/nofeedback\ condition$) was expressed by using ratios. This represented a condition in which pain was not influenced by alterations in the arm's image, but it could still consider the presence of the VR environment effect. Vividness and unpleasantness responses (both from 0 to 100) were not normalised.

Epoching, band-pass filtering and analysis of EDA of the main experiment were performed off-line using AcqKnowledge® Acquisition and Analysis software (Biopac). Data pre-processing included 30 Hz waveform resampling, median smoothing, 1 Hz FIR filter and smoothing baseline removal. The identification of outliers was conducted using the interquartile range method on an individual subject basis. Both SCL mean values and SCR amplitude values were extracted. Values greater or smaller than 1.5 times the interquartile range were considered outliers and subsequently removed. The no feedback normalisation was used also for EDA values ($nSCL = SCL\ mean\ value_{condition}/nofeedback\ condition$; $nSCR = SCR\ amplitude\ value_{condition}/nofeedback\ condition$). Baseline data were not included in the analysis.

Inferential statistics was performed with the statistical software Jasp (0.16.1.0) and Matlab (R2022a). In the initial phase, we decided to investigate potential differences in subjective evaluations. Considering the non-normal distribution of data (Shapiro-Wilks test), pain NRS responses and Unpleasantness responses were analysed as dependent variables with a Friedman test, a “rmAnova-like” test with the factor “*Visual feedback*” (6 levels). Vividness responses were analysed in a similar fashion but using a parametric test.

Due to missing data in the EDA responses database after outliers' removal, we decided to employ a Generalized Linear Mixed Model (GLMM). However, this required computational simplification. Therefore, we used three dummy variables to model the visual feedback based on three main factors: hand visibility (normal or altered), arm length (normal or altered), and lesion (absent or present). This approach allowed us to cluster all the conditions and assign a code to each of them by using 0 (normal visibility, normal length, absent injury) and 1 (altered visibility, altered length, present injury). As GLMM require values >1 , we decided to add 1 to all the computed values. The GLMM family and link function were chosen based on the lowest Akaike information criterion (AIC) (Barber & Thompson, 2004).

nSCL values were analysed with GLMM using an inverse gaussian family with a log link function. Participants were modeled as a random effect factor, while hand visibility, arm length, injury, vividness, and unpleasantness were considered fixed effect factors. nSCR values were analysed with GLMM using a normal family with a log link function. Factors were modeled as for nSCL.

To remain consistent with the analysis of physiological measurements, we conducted a second analysis of subjective measurements using similar models. However, EDA can be a direct measure of arousal in response to vividness and unpleasantness, while the subjective assessment of perceived pain (NRS) relates solely to pain (the question is specifically 'How much pain did you experience?'). In other words, vividness and unpleasantness can have a direct effect on EDA but may only correlate with the NRS responses. For this reason, we decided not to include vividness and unpleasantness in the NRS pain responses analysis model. Therefore, the model includes subjects as random factors and visual feedback modulations, namely Hand visibility, Length, and Injury as fixed factors. nNRS values were analysed with GLMM using a normal family with a log link function. The same model was used with Vividness and Unpleasantness which are believed to be influenced by visual feedback modulations. Vividness responses were analysed GLMM using a gamma family with log link function, whereas Unpleasantness with gamma family with log link function.

For correlation analysis, Spearman's rank correlation (ρ) was calculated between nNRS responses and Unpleasantness; nNRS responses and nSCL responses; nNRS and nSCRs; nNRS responses and Vividness; nSCL and Vividness.

Visual feedback (factors)						
Injury	Absent (0)	Present (1)	Absent (0)	Present (1)	Present (1)	Absent (0)
Length	Normal (0)	Normal (0)	Altered (1)	Normal (0)	Altered (1)	Normal (0)
Hand vision	Normal (0)	Normal (0)	Normal (0)	Altered (1)	Altered (1)	Altered (1)

Figure 15, Visual feedback alterations and codes used in the analysis. From left to right: normal, characterised by absent injury, normal length, and normal hand visibility (000); injury (100), characterised by present injury, normal length, and normal hand visibility; telescoping (010), characterised by absent injury, altered length, and normal hand visibility; trans-radial (101), characterised by present injury, normal length, and altered hand visibility; trans-humeral (111), characterised by present injury, altered length, and altered hand visibility; blurring (001), characterised by absent injury, normal length, and altered hand visibility.

6.4 Results

Pilot experiment

The pain NRS responses were found significantly different from 0 (mean \pm SD: 2.38 ± 1.18 , $t=7.023$, $p<.001$). SCRs differed between touch and pain conditions (mean \pm SD: 0.07 ± 0.06 vs 0.22 ± 0.20 , $t=-2.764$, $p=0.022$). The correlation between SCRs and pain NRS responses was positive ($r=0.73$, $p=0.01$).

Principal experiment

The Friedman ANOVA test conducted on all pain nNRS responses did not show any significant difference between conditions ($\chi^2(5)=0.112$, $p=1.000$). The same analysis for Unpleasantness showed significant differences in responses ($\chi^2(5)=31.323$, $p<.001$). Conover's post-hoc comparisons, adjusted with Holm correction, showed that *Telescoping*, *Trans-radial* and *Trans-humeral* conditions were perceived as more unpleasant than *Normal* condition (telescoping mean \pm SD: 27.61 ± 25.70 vs 10.72 ± 13.14 , $tStat=3.256$, $p=0.019$; trans-radial mean \pm SD: 31.89 ± 25.87 vs 10.72 ± 13.14 , $tStat=4.559$, $p=<.001$; trans-humeral mean \pm SD: 30.72 ± 28.17 vs 10.72 ± 13.14 , $tStat=3.675$, $p=0.005$);. Moreover, *Trans-radial* condition was perceived more unpleasant than *Blurring* condition (mean \pm SD: 31.89 ± 25.87 vs 14.00 ± 15.18 , $T-Stat=3.722$, $p=0.005$). rmANOVA conducted on Vividness responses showed significant differences between conditions ($F(5)=2.934$, $p=0.017$). Post-hoc comparison's, adjusted with Holm correction, showed that the *Normal* condition was perceived as more vivid than the *Telescoping* condition (mean \pm SD: 48.06 ± 22.89 vs 34.50 ± 22.63 , $t=3.211$, $p=0.028$) and the *Blurring* condition (mean \pm SD: 48.06 ± 22.89 vs 35.28 ± 26.15 , $t=3.027$, $p=0.046$).

The GLMM analysis on nSCL evidenced a significant main effect of *Injury* (Figure 16), which if present decreases SCL (effect=-0.0342, tStat(868)=-4.517, p<.001); a main effect of *Hand visibility* (Figure 16), which if altered decreases SCL (effect=-0.0551, tStat(868)=-7.114, p<.001); and a main effect of *Unpleasantness*, which increases SCL (effect=0.0004, tStat(868)=2.078, p=0.037). The interaction between the fixed effect of *Injury* and *Unpleasantness* was significant (Figure 16) showing a further decrease in SCL (effect=-0.0004, tStat(868)=-2.036, p=0.041). The same applies to the interaction between *Length* and *Unpleasantness* (Figure 16) (effect=-0.0008, tStat(868)=-4.5767, p<.001).

The interaction between the fixed effect of *Vividness* and *Injury* (Figure 16) (effect=0.0008, tStat(868)=5.023, p<.001) and between *Vividness* and *Hand visibility* (Figure 16) (effect=0.0003, tStat(868)=2.201, p=0.027) were significant, showing a reduction of the decrease in SCL in both cases.

The GLMM analysis on nSCR evidenced a significant main effect of *Length* (Figure 17), which if altered decreases SCR amplitude (effect=-0.2163, tStat(816)=-3.720, p<.001); and a main effect of *Hand visibility* (Figure 17), which if altered decreases SCR amplitude (effect=-0.1397, tStat(816)=-2.445, p=0.014). The interaction between the fixed effect of *Vividness* and *Length* (Figure 17) (effect=0.0039, tStat(816)=2.783, p=0.005) is significant, showing a reduction of the decrease in SCR amplitude. The interaction between the fixed effect of *Vividness* and *Hand* (Figure 17) (effect=0.0025, tStat(816)=2.058, p=0.039) is significant, showing a reduction of the decrease in SCR amplitude.

The GLMM analysis on nNRS evidenced a significant main effect of *Injury* (Figure 18), which if altered decreases NRS responses (effect=-0.0786, tStat(104)=-2.112, p=0.037); and a main effect of *Hand visibility* (Figure 18), which if altered increases NRS responses (effect=0.1640, tStat(104)=4.375, p<.001).

The GLMM analysis on Vividness responses did not evidence any statistically significant effect (F(3)=1.053, p=0.372). The GLMM analysis on Unpleasantness responses evidenced a significant main effect of *Injury* (effect=0.5298, tStat(104)=3.734, p<.001), and *Length* (effect=0.3710, tStat(104)=2.615, p=0.010) showing an increase in Unpleasantness when the injury is present and the length is altered.

nNRS responses positively correlated with Unpleasantness ($\rho=0.33$, p<.001) and negatively correlated with nSCL responses ($\rho=-0.38$, p<.001). The correlation between nNRS responses and Vividness was not statistically significant ($\rho=0.14$, p=0.15), the same applies to nNRS and nSCRs ($\rho=0.03$, p=0.31) and to nSCL and Vividness ($\rho=-0.07$, p=0.02).

Effect of predictors on SCL

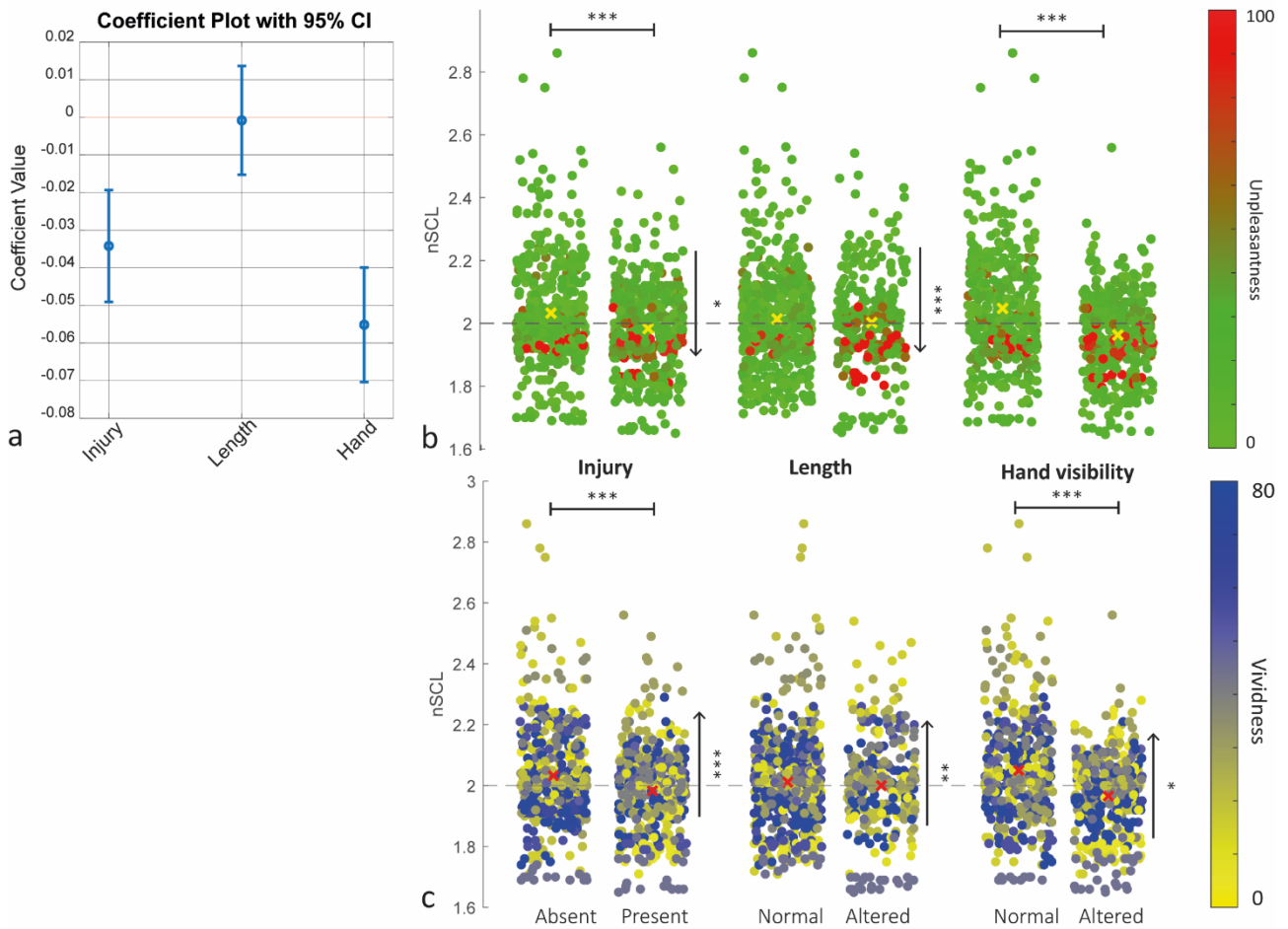


Figure 16, Coefficient plot and scatter plot of predictors effects in Generalized Linear Mixed Model (GLMM) of normalised Skin Conductance Level (nSCL). a) Coefficients below 0 indicate significant negative effect on the dependent variable nSCL (Injury and Hand visibility), coefficients between positive and negative values indicate non-significant mixed effect (Length). b) Scatter plots of main factors Injury, Length, Hand visibility and interaction with Unpleasantness. Dots are nSCL values influenced by high (red) or low (green) Unpleasantness levels. Asterisks represent statistical significance of the effect of factors (or predictors), arrows indicate the direction of the effect of interactions on nSCL: ***p < .001, **p < .01, *p < .05. Yellow crosses represent mean values. The presence of injury decreases the nSCL, the Unpleasantness increases the effect of the presence of Injury, further decreasing the nSCL. The length alteration effect is not statistically significant, but its interaction with Unpleasantness significantly decreases the nSCL. The alteration of hand visibility decreases the nSCL, but there is no interaction with Unpleasantness. c) Scatter plots of main factors Injury, Length, Hand visibility (as above) and interaction with Vividness. Dots are nSCL values influenced by high (blue) or low (yellow) Vividness levels. Asterisks represent statistical significance of the effect of factors (or predictors), arrows indicate the direction of the effect of interactions on nSCL: ***p < .001, **p < .01, *p < .05. Red crosses represent mean values. Vividness decreases the effect of the presence of Injury, thus increasing nSCL; it also decreases the effect of length alteration, increasing nSCL; and decreases the effect of hand visibility alteration, increasing nSCL.

Effect of predictors on SCR

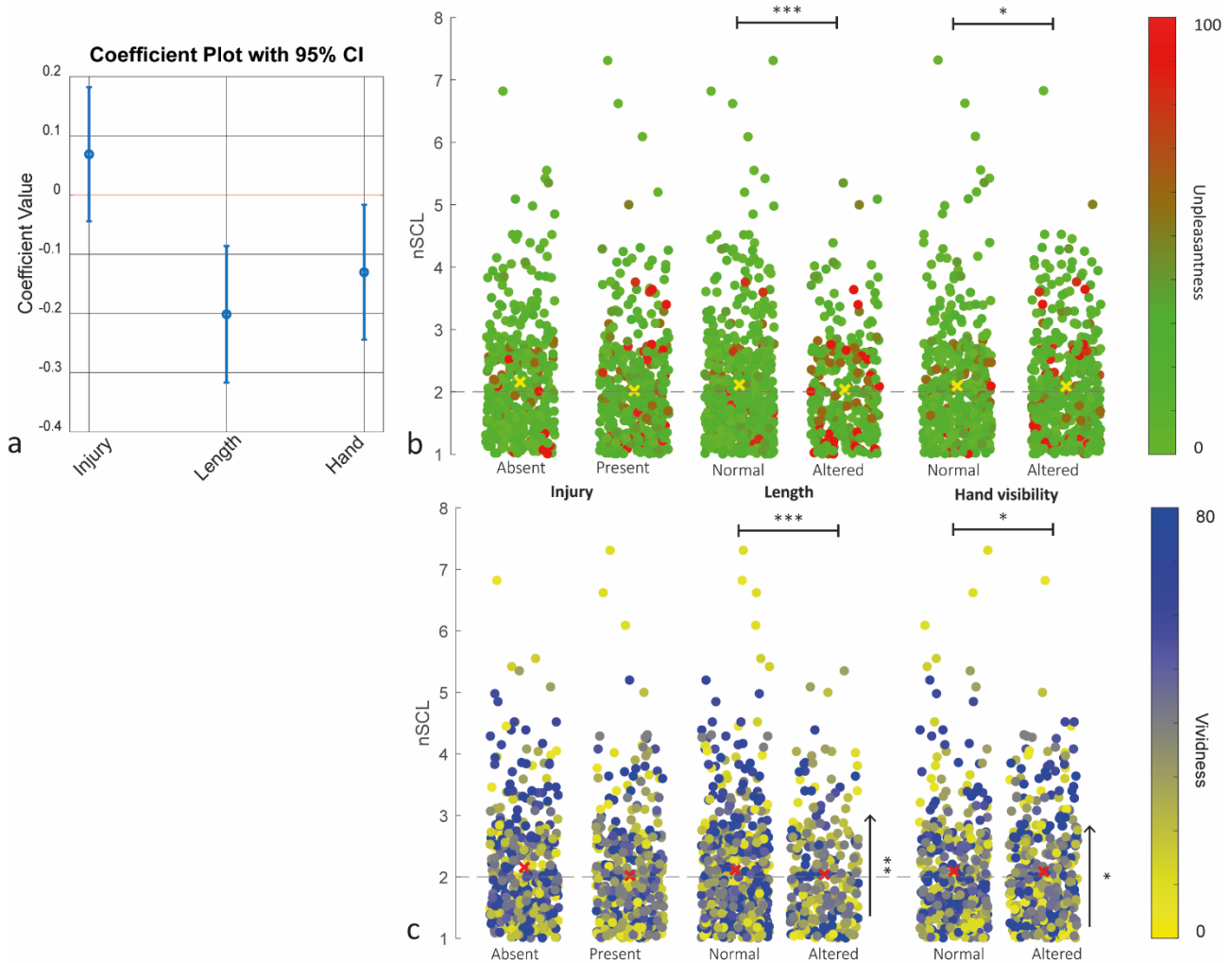


Figure 17, Coefficient plot and scatter plot of predictors effects in Generalized Linear Mixed Model (GLMM) of normalized Skin Conductance Responses (nSCRs). a) Coefficients below 0 indicate significant negative effect on the dependent variable nSCRs (Length and Hand visibility), coefficients between positive and negative values indicate non-significant mixed effect (Injury). b) Scatter plots of main factors Injury, Length, Hand visibility and interaction with Unpleasantness. Dots are nSCR values influenced by high (red) or low (green) Unpleasantness levels. Asterisks represent statistical significance of the effect of factors (or predictors): *** $p < .001$, ** $p < .01$, * $p < .05$. Yellow crosses represent mean values. The presence of injury effect is not statistically significant. The length alteration decreases the nSCRs; the alteration of hand visibility decreases the nSCRs. No interaction of factors with Unpleasantness are significant. c) Scatter plots of main factors Injury, Length, Hand visibility (as above) and interaction with Vividness. Dots are nSCR values influenced by high (blue) or low (yellow) Vividness levels. Asterisks represent statistical significance of the effect of factors (or predictors), arrows indicate the direction of the effect of interactions on nSCRs: *** $p < .001$, ** $p < .01$, * $p < .05$. Red crosses represent mean values. Vividness decreases the effect of the length alteration, increasing nSCRs; decreases the effect of hand visibility, increasing nSCRs.

Statistical Table 3

Correlation	p-value	Spearman's rho
nNRS - Unpleasantness	$p < .001$	$\rho = 0.33$
nNRS - nSCL	$p < .001$	$\rho = -0.38$
nNRS - Vividness	$p = 0.15$	$\rho = 0.14$
nSCL - Vividness	$p = 0.02$	$\rho = -0.07$
nNRS - nSCRs	$p = 0.31$	$\rho = 0.03$

Table 3, Statistical table of the correlation tests performed with corresponding p-values and correlation coefficients.

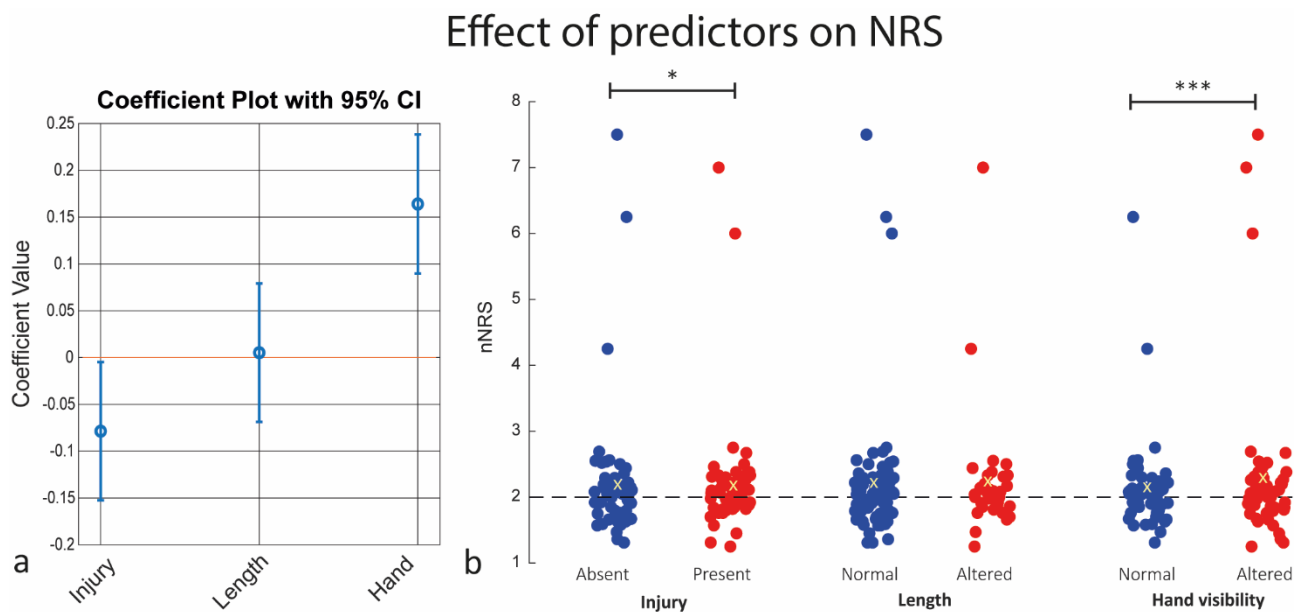


Figure 18, Coefficient plot and scatter plot of predictors effects in Generalized Linear Mixed Model (GLMM) of normalized Numerical Rating Scale (nNRS). a) Coefficients below 0 indicate a significant negative effect on the dependent variable nNRS (Injury), coefficient between positive and negative values indicate non-significant mixed effects (Length), coefficients above 0 indicate a significant positive effect (Hand visibility). b) Scatter plots of main factors Injury, Length, Hand visibility. Asterisks represent statistical significance of the effect of factors (or predictors): *** $p < .001$, ** $p < .01$, * $p < .05$. Yellow crosses represent mean values. The presence of injury decreases nNRS values, the length alteration effect is not statistically significant, the alteration of hand visibility increases the nNRS values.

6.5 Discussion

The relationship between body representation and pain is a complex and multifaceted one, and may involve physiological, cognitive, and affective factors. In the scientific literature, numerous cases are reported where observing one's own body or a part of it can reduce the perceived pain intensity (Mancini et al., 2011; Romano et al., 2014). On the other hand, concealing or altering the body image can exacerbate pain as showed by lowered pain thresholds (Osumi et al., 2014). The modulatory effect of visual feedback could play a role in phantom limb pain, where following amputation and incongruence between sensory feedback, patients often experience debilitating pain associated with the sensation of the presence of the lost limb (Ramachandran & Hirstein, 1998b; Ramachandran & Rogers-Ramachandran, 1996).

With this perspective, we aimed to artificially recreate a pain that could be associated with the modification of body image. For this reason, we decided to induce a pain of identical intensity across all conditions, distinguishable solely by its interaction with visual feedback. Although our pain – resembling nociceptive pain – was externally induced, with the objective of mimicking neuropathic pain (as in Phantom Limb Pain) we did not disclose the source of the pain (the pinprick device was not shown in the VR environment). In this manner, participants would be more likely to associate the pain with the alteration of their body image.

Noxious stimuli activate A δ and C nociceptors, which are typically assessed by brain potentials evoked by laser, thermal, mechanical, electrical, and chemical stimuli (Baumgärtner, Greffrath, & Treede, 2012; Madsen, Finnerup, & Baumgärtner, 2014). Recently, pinprick potentials (PEPs) have been widely employed in the study of neuropathic pain, particularly to investigate mechanisms such as secondary hyperalgesia (Valentini & Schulz, 2020) and central sensitisation (Scheuren, Rosner, Curt, & Hubli, 2020; van den Broeke et al., 2015). Skin conductance responses (SCRs) can also be employed to investigate the vegetative response to pain: SCR values are increased by central sensitisation mechanisms and positively correlate with an increase in perceived pain (Salameh, Perchet, Hagiwara, & Garcia-Larrea, 2022). In our pilot study, the results obtained from a comparison between tactile and painful stimuli showed that, alongside differences in pain subjective ratings, the skin conductance responses (SCRs) elicited by the customised device we used are sensitive to differences between touch and pain. Furthermore, the positive correlation observed between autonomic response and subjective perception of pain supports previous findings and the utility of this method for studying the indirect response to pain.

After ensuring that our device could induce pain and reliably measuring it through electrodermal activity (EDA), we used this method to investigate differences in perception and autonomic responses

induced by alterations in body image. Here, experimental pain changes appear to be caused not only by the visual feedback modulation but seems to be the result of an extremely complex network involving subjective factors, body image discomfort, and quality of the VR immersivity experience. From our model, it emerges that the pain perceived by the subject can be directly exacerbated by the alteration of hand visibility. In this context, participants were stimulated on the back of the hand but could not see the source of the pain. Based on existing literature, one could speculate that if the instrument used to evoke pain had been visible, there might have been an analgesic effect. In our case, when the hand was poorly visible or not visible at all (*blurring*, *trans-radial*, and *trans-humeral* conditions), there was a worsening of perceived pain compared to when it was clearly visible (*normal*, *telescoping*, and *injury* conditions). This hyperalgesia effect appears to be correlated with a greater decrease in tonic EDA (Skin conductance level, SCL). However, although the phasic component (Skin conductance response, SCR) also decreases when the hand visibility is altered, is not correlated to the perceived pain.

Hence, poor hand visibility has a direct decreasing effect on both SCL and SCRs. However, while the presence of the injury seems to only affect SCL, altered length affects only SCRs. These differences may be explained by the fact that the tonic component (SCL) and the phasic component (SCR) may reflect different cognitive and affective processes, with the former being more responsive to general emotional tone and the latter having a more attentive nature (Braithwaite, Brogna, & Watson, 2014). It is possible, therefore, that different types of feedback activate different cognitive and affective functions, or they activate the same functions but to varying degrees.

It is intriguing that the effect of visual feedback alterations on autonomic responses is dampened by vividness, such that the greater the vividness resulting from the virtual condition, the more pronounced the damping effect. From our initial analysis of subjective measures, it emerges that the *normal* condition is more vivid than the *telescoping* and *blurring* conditions, which respectively involve altered length and hand visibility. As previously mentioned, these effects reduce SCL and the amplitude of SCRs. This would suggest that higher vividness may be associated with higher levels of SCL or SCRs. However, our analysis does not reveal such correlations. On the contrary, a previous study seems to suggest the opposite relationship, where higher self-identification is associated with a greater decrease in SCL (Romano et al., 2014). It is essential to consider that in that study, conditions were compared where identification could occur with a human body or not, whereas in our case, all compared conditions involve a human avatar. Furthermore, differences could also be explained by the methods used to assess self-identification being different.

Another piece of the puzzle is the unpleasantness associated with body image. This does not seem to be predicted by poor hand visibility, but the analysis reveals an effect of altered length and presence

of injury disclosing an indirect effect of these factors on pain. Furthermore, the greater the unpleasantness, the more pronounced the effect of visual feedback on the autonomic response. Indeed, unpleasantness enhances the decreasing effect of the presence of the injury on SCL, and even though altered length alone does not seem to influence SCL, when associated with higher unpleasantness levels, the decrease in SCL becomes evident. Interestingly, it also has a direct positive effect on SCL, slightly increasing its level. Although this may appear counterintuitive in these circumstances, it is possible that it plays the role of a general arousal activator. At this point, it is necessary to remember that EDA is a nonspecific response to pain and reflects a more general physiological arousal. Unpleasantness is also positively correlated with perceived pain, meaning that greater discomfort corresponds to greater pain. The conditions that deviated the most from the normal condition in terms of unpleasantness were *telescoping*, *trans-radial*, and *trans-humeral*, suggesting that the further one deviates from a normotypical appearance, the greater the discomfort experienced. In this complex scenario it is extremely challenging to disentangle the different contributions of each component and some points remain poorly understood. For example, why does the autonomic response decrease rather than increase in response to changes in visual feedback and unpleasantness? One hypothesis is that, similarly to what has been previously reported (Matamala-Gomez et al., 2020) there may have been an effect of pain anticipation that modulated the autonomic response. In our case, the altered view of the body before stimulation might heighten expectancy regarding the impending sensory pain experience, but later reduce the overall saliency and, in turn, the sensory response to the subsequent painful stimulation (Iannetti & Mouraux, 2010; Romano & Maravita, 2014). Another hypothesis is that the altered body image acted as a stressor, causing the activation of the descending analgesic neural pathways (Crofford & Casey, 1999) adequate to trigger an attenuation of the sympathetic response but not sufficient to cause a perceivable analgesia in the subject. This would also explain why the injury condition appears to be the only one inducing a reduction in perceived pain. Although entirely speculative, one could hypothesise that only the presence of the injury is so activating as to result in a perceivable analgesia.

6.6 Conclusions

One of the causes of phantom limb pain appears to be the incongruence between the body's representation and its actual image. The absence of visual feedback seems to play a significant role in pain perception. Here we investigated the effect of visual feedback alterations on pain in a VR environment. While caution is necessary in interpreting the results considering the use of a virtual apparatus and the potential impact of embodiment on them, our findings showed the co-participation

of visual feedback alterations and discomfort elicited by the resulting body image in modulating pain. Although presence of the injury and alteration of length also have an impact on the autonomic response, they seem to impact only indirectly the perceived pain. In fact, it appears that direct impact is attributed to poor hand visibility. Given that in our experiment, pain was applied to the hand, and the lack of hand visibility resulted in exacerbation of perceived pain and decrease in autonomic response, it becomes evident that not being able to clearly attribute the source of pain can intensify it. In this perspective, the failure to identify the source of pain rather than the absence of visual feedback itself could be the cause of pain and offer a new way to interpret phantom limb pain. Further investigations are necessary. Ideally, it would be valuable to provide the patient with a visible source of pain and explore its potential modulatory effect. This study contributes to the understanding of phantom limb pain and may facilitate future comprehension of the interplay between cognitive-affective and physiological mechanisms of neuropathic pain.

7 Integration of Proprioception in upper limb prostheses through non-invasive strategies

7.1 Critical review of the literature

Background

Upper limb amputations affect millions of people worldwide. A recent estimation from Global Burden of Disease studies stated that in 2017 more than 20 million people were living with an upper limb amputation due to traumatic causes, including 11.3 unilateral and 11 bilateral million amputation cases. These represent 19.6% and 19.1%, respectively of the 57.7 million cases considering all levels of amputation reported (McDonald, Westcott-McCoy, Weaver, Haagsma, & Kartin, 2020). While peripheral arterial disease and diabetes account for the majority of lower limb amputations worldwide, the most common causes for upper limbs depend on the geographical region of occurrence (Behrendt et al., 2018). In developing countries, trauma is the primary cause of amputations for people under the age of 50 (Atkins, Winterton, & Kay, 2008), and in the vast majority of cases (90-92%) it results from industrial accidents (Fitzgibbons & Medvedev, 2015; Freeland & Psonak, 2007).

The currently available types of prostheses include cosmetic prostheses, light but not useful for replacing lost motor functions, and functional body-powered and myoelectric prostheses. Conflicting results have been found in terms of the relative performances of the latter group, with no conclusive evidence in favour of one of them (Carey, Lura, Highsmith, Cp, & Faaop, 2015). Two out of three upper limb amputees report a high level of dissatisfaction with their current prosthesis (Davidson, 2002), both in terms of performance and comfort (Smail, Neal, Wilkins, & Packham, 2021).

Users exploit sounds and vibrations coming from the motors and the torques transmitted by the socket as a source of somatosensory information to control the prosthesis. However, together with slow and noisy mechanics, unsatisfactory wearability, and poor dexterity issues, the lack of purposely delivered sensory feedback represents a critical limitation and reason for the refusal of the device (Cordella et al., 2016; Pylatiuk, Schulz, & Döderlein, 2007). Not only the lack of feedback affects prosthesis control, but it is also likely to be one of the causes of poor integration of the prosthesis in the body schema of the user, affecting its acceptability and user's confidence (Blanke, 2012; D'Alonzo & Cipriani, 2012; Makin, de Vignemont, & Faisal, 2017).

Sensory feedback includes both exteroceptive senses, providing us information about the environment, and proprioception. The broad spectrum of proprioception includes the senses of position and body movement, together with the sense of the force exerted and objects' heaviness

(Proske & Gandevia, 2012). Previous works on artificial feedback in prosthetics mostly focused on the restitution of touch, but relatively fewer studies addressed how to provide proprioceptive information. Also, a critical overview of this topic is still missing. Here, after discussing how the neurophysiology of proprioception may be artificially recreated with the available technology, we provide a review of the studies where non-invasive strategies are employed to provide proprioceptive feedback in arm and hand prostheses. We included kinematics and dynamics studies, in which position and motion information alone or supplemented by force information is returned, respectively. Finally, we discuss the main findings and limits of these studies, together with some proposals to be possibly implemented in future studies.

Natural & Artificial: Extracting and Translating Proprioception

Developing from the concept of muscular “receptivity”, i.e., the body acts as a stimulus for its own receptors (Sherrington, 1907), despite the lack of an agreed-upon definition, the most widely accepted has proprioception to include the sense of position and movement, sense of tension or force, sense of effort, and sense of balance (Proske & Gandevia, 2012). Proprioception is built through the summation of inputs from several peripheral receptors, providing a unique percept. Muscle spindles, however, play a key role in providing body posture and movement, whereas Golgi tendon organs (GTOs) account for the sense of tendon tension and muscle load. Likewise, following the amputation and the loss of these receptors, ideally, the same type of information should be extracted from purposely instrumented prostheses (Figure 19).

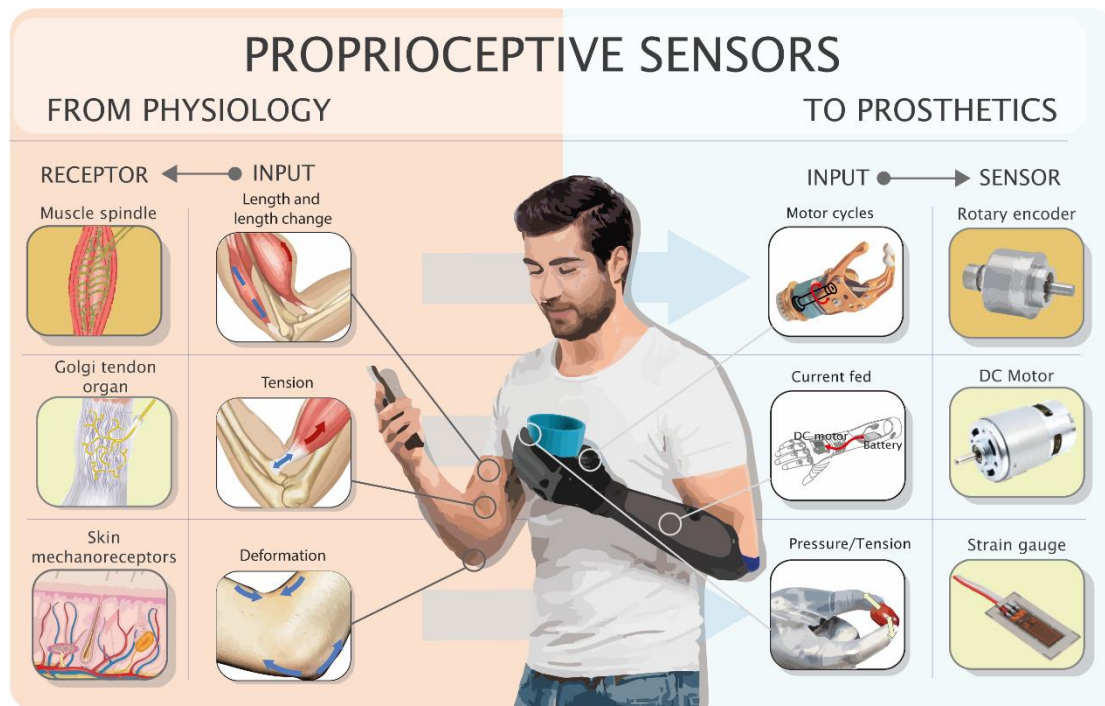


Figure 19, Graphic comparison between physiological and artificial transduction of proprioceptive information. The outer columns show how the function of the receptors in our body (left) could be emulated by some of the common sensors already available on the market (right). In prosthetics, the employed hardware dictates the strategies to be implemented (inner columns) and the input signal may differ from the one coded by the physiological receptor. For instance, the number of cycles of the motors extracted by rotary encoders is used instead of the muscle length, while the current to the motors may replace tendon tension, as an alternative to a tension sensor, which is less common and would need to be purposefully integrated into the device additionally.

Information on Position & Movement

Muscle spindles are stretch-sensitive mechanical receptors found virtually in all skeletal muscles, except for most facial muscles (Cobo, Abbate, de Vicente, Cobo, & Vega, 2017; May, Bramke, Funk, & May, 2018). Muscle spindles follow length changes of the parent muscle so that the firing rate of their sensory innervation is proportional to the length of the fibres as well as the rate of length change itself. The functional unit of the receptor is formed by a bundle of specialized muscle fibres encapsulated by a connective tissue capsule, called intrafusal fibres, and divided into Bag (Bag1, Bag2), and Nuclear Chain fibres. These receptors, given the length and length change sensitivity, are thought to inform of both position and movement senses (Proske & Gandevia, 2012). In particular, Group II afferent fibres innervating Bag2 and Nuclear chain fibres are responsible for constant length monitoring, while Group Ia afferents, innervating the fibres of the whole spindle, including Bag1 type, respond also the rate of length change. Such a difference depends also on the type of efferent innervation of the intrafusal fibre, being static gamma-motor neurons for the former group and dynamic gamma-motor neurons for Bag1 fibres (Macefield & Knellwolf, 2018). Efferent fusimotor innervation, indeed, elicits the contraction of the polar regions of intrafusal fibres and thereby regulates the tension of the central sensory region (Macefield & Knellwolf, 2018; Proske, 1997). In

prosthetics, the sensors employable to extract kinaesthetic information depend both on the preferences of the designer, and, most of all, on the actuators (i.e., devices converting energy into motion and force) operating the prosthesis. For instance, incremental magnetic encoders embedded on the motors were employed to provide finger position monitoring, acting like cybernetic hand muscle spindles (Carrozza et al., 2006). In this case, the number of cycles of the motor (the higher the number of cycles, the greater the movement of the end-effector, i.e., the finger) is transduced in place of the muscle length. A biomimetic approach, trying to reproduce muscle spindles artificially, has also been attempted (Jaax & Hannaford, 2002; Shin et al., 2016) and several mathematical models have been made (Mileusnic, Brown, Lan, & Loeb, 2006) to simulate the different response dynamics of intrafusal fibres, but to date, no examples of their application in prosthetics are known to the authors. Cutaneous mechanoreceptors in superficial and deep layers of the skin contribute to kinaesthetic senses (Collins, Refshauge, Todd, & Gandevia, 2005), providing signals to be integrated with the information coming from the spindles of the muscles acting on one joint, as well as information from mechanoreceptors present in the joint itself (Bosco & Poppele, 2001; Ribot-Ciscar, Bergenheim, & Roll, 2002). Indeed, the movement of a joint is accompanied by a pattern of skin strain and deformation that varies with the speed and amplitude of the movements, which is then translated into neural signals by the mechanoreceptors through their coupling of semirigid connective tissue structures and nervous terminals (Johnson, 2001). Rapidly adapting Meissner and Pacinian corpuscles, are known, for example, to be involved in the detection of finger joints movement (Edin & Abbs, 1991). The function of these receptors has been extensively reproduced artificially, both through a biomimetic approach and by using more common electronic sensor technology. However, despite the capability of skin mechanoreceptors to transduce both exteroceptive and proprioceptive movement-related stimuli, artificial counterparts, like strain gauge or piezoelectric sensors, have been mostly employed for providing touch information and for texture recognition, leaving aside the potential application in proprioception substitution (Masteller et al., 2021; Oddo et al., 2016; Raspopovic et al., 2014; Zangrandi, D'Alonzo, Cipriani, & Di Pino, 2021).

Building on the physiological basis of proprioception is a potential strategy to approach sensory feedback. Spindle afferents can be, indeed, activated through tendon vibration evoking a so-called kinaesthetic illusion or tendon-vibration illusion (TVI). Vibration affects spindle afferents, whose firing is entrained to the same rate as the one of the stimuli, creating the sensation of muscle stretch and, thus, the illusion of movement in the direction that would elongate the vibrated muscle (Goodwin et al., 1972). A similar phenomenon also occurs when a mechanical stretch stimulation is applied to the skin close to a joint. These paradigms are currently being investigated as possible strategies to relay prosthesis proprioceptive-like information to the user (e.g., 34, *see below*).

Information on Force, Tension & Effort

Golgi tendon organs (GTOs) are mechanoreceptors located in series with the muscle at the transition region between muscle fibres and tendons (Jami, 1992). Each GTO is innervated by one single Ib large diameter rapidly-conducting afferent fibre, that responds to active tension of the muscles and to changes in contractile force in discrete steps, reflecting the recruitment of additional motor units (motoneuron + innervated muscle fibres) (Davies, Petit, & Scott, 1995). Sense of effort refers to the sensation experienced when engaging in motor activities, which are directly related to the task being executed and refers to the force muscles need to generate to complete such task. It is thought to be generated centrally, through the transmission of the efference copy (Angel, 1976), an “internal copy” of the motor command. Sense of tension or force (the perception of the amount of external resistance that must be overcome to perform a particular task) comes from the activation of GTO, together with muscle spindles contribution. Finally, evidence suggests that heaviness sensation can be generated either centrally or peripherally, possibly influenced by what the subject focuses their attention on (Proske & Allen, 2019).

Either biomimetic or more conventional strategies can be used to sense the force exerted by the prosthesis. In the former case, for example, tension sensors mimicking the behavior of GTOs in the cable transmission have been used to monitor the force applied by a sensorised myoelectric hand (Carrozza et al., 2006). Alternatively, it is possible to measure the current fed to the prosthetic motor and put it in relation to the angular displacement of the end-effector to calculate the contact stiffness (Deng, Xu, Zhuo, & Zhang, 2020). However, in commercial devices, the EMG-driven direct current (DC) motors are not equipped with any intrinsic sensor (Belter, Segil, Dollar, & Weir, 2013). Finally, given that the relation between object stiffness and surface deformation is related to the applied pressure, superficial resistive sensors can also be used to indirectly measure the grip force applied by an artificial hand (Masteller et al., 2021).

While a vibrotactile device can generate a kinaesthetic sensation by stimulating spindle afferents (i.e., homomodal stimulation, *see: Restitution of Proprioception*), a force and heaviness sensation cannot be elicited in a homomodal way with current technology. This could definitely represent an issue to be addressed in future works.

Restitution of Proprioception

To provide the users with proprioceptive feedback from the prostheses, these should be equipped with appropriate sensors that extract information on positions and forces, as well as encoding algorithms and stimulators that convey the encoded pattern to the remaining functional sensory system of the user (Figure 20). This complex process represents a great challenge, especially because of the low efficacy of the artificial interfacing system, flawed by: i) the time consuming signal processing and transmission of information from the device to the user (Sensinger & Dosen, 2020); ii) the area required to place all the components often disproportionately large compared to the available skin surface (*see below*) (Demolder, Molina, Hammond, & Yeo, 2021); iii) the repeated calibrations of the stimulation parameters, needed for a reliable user's sensation and perception (Boljanić et al., 2022; Isaković, Malešević, Keller, Kostić, & Štrbac, 2019).

Sensory restitution can be achieved through invasive or non-invasive strategies. We circumscribed our critical analysis to non-invasive strategies, excluding studies involving implantation surgery and manipulation of the patient's anatomy (Grushko, Spurný, & Černý, 2020; Masteller et al., 2021; Raspopovic, Valle, & Petrini, 2021).

In line with the literature, feedback is defined as *homomodal* when the artificial stimulus delivered to the user belongs to the same sensory system and modality conveying the missing information (e.g., conveying touch with devices that provide pressure feedback). On the contrary, *heteromodal* feedback or sensory substitution exploits a sensory channel that is different from the one employed physiologically (e.g., providing angular movement through hearing), or the same channel but changing the modality of the input stimulus (e.g., providing limb position through vibration in place of skin stretch).

Another important point relates to the body part used to reconstitute the feedback. Obviously, *homotopic* feedback - provided to the very same site of the body to which the information pertains- is not feasible in amputees due to the lack of the limb, thus *heterotopic* stimulation is mostly employed. An intriguing further possibility to approximate *homotopic* restitution is to exploit body territories that, when touched, provide sensations that the amputee refers to the lost limb (Di Pino et al., 2020a; Zollo et al., 2019). Such a referred sensation phenomenon, present in most amputees stump, neck and face, results from central and peripheral neural rearrangement (Di Pino et al., 2009).

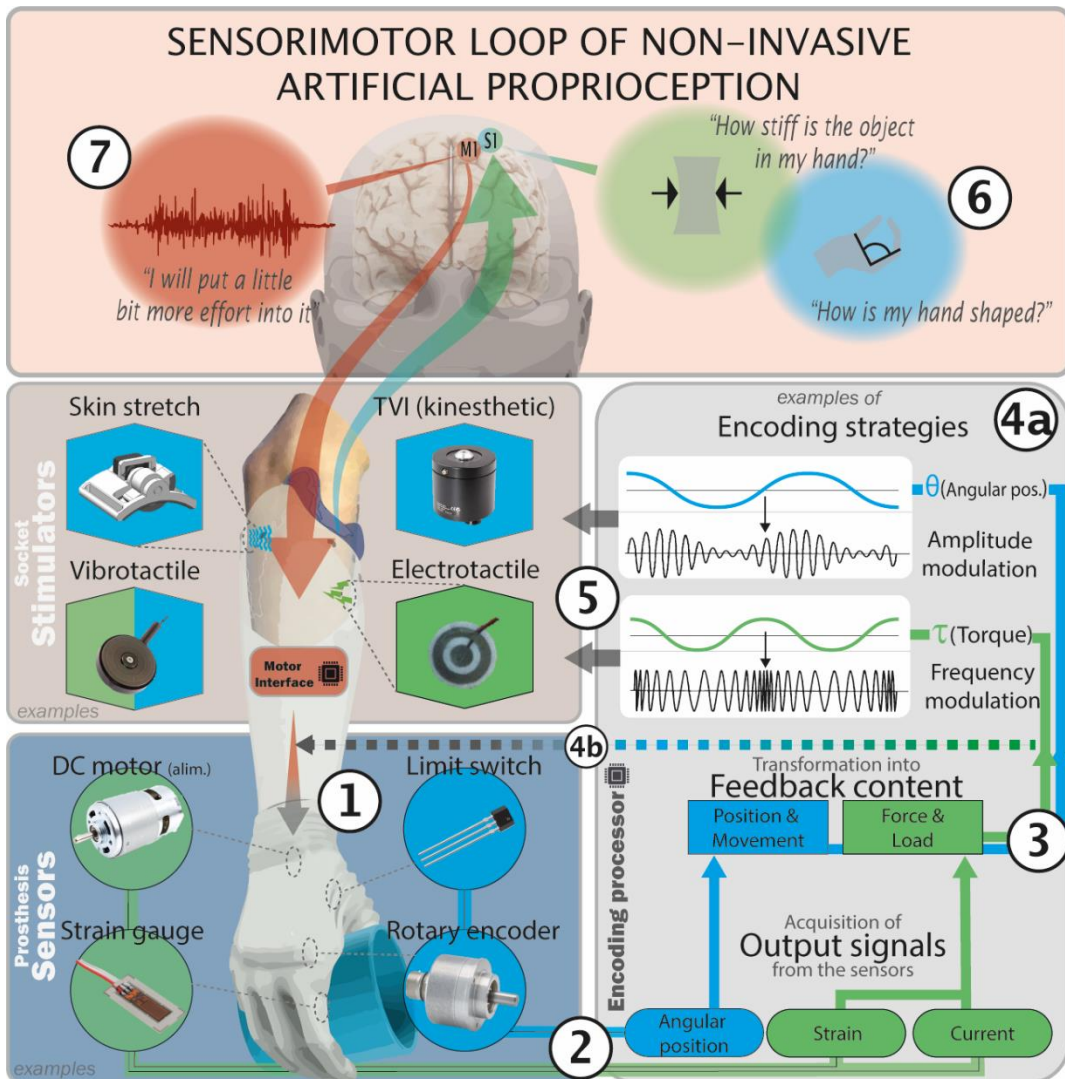


Figure 20, Acquiring and encoding proprioceptive info for sensorimotor integration in prosthetics. 1. The actuator of the prosthesis operates the end effector based on the uptaken biologic signals of the user (e.g., EMG activity through surface electrode in case of myoelectric devices); 2. Sensors embedded in the prosthesis extract the configuration and power developed by the device (e.g., the joint angle is uptaken by the rotary encoders, pressure by superficial sensors and the force exerted is derived from the current adsorbed by the motors), also accordingly with the interaction with the environment (e.g., the cup grasped); 3. Data acquired from the sensors, which refer to proprioceptive-like parameters characterizing the state of the device are translated into feedback content to be delivered to the user; 4a. The feedback content is encoded back into input signals for the stimulators, on the basis of the amount of information to be transmitted, as well as the hardware's capacities; 4b. The prosthesis, if implemented, can automatically modify (reflex-like behavior) the motor output based on the uptaken data; 5. The stimulators integrated into the device socket deliver the information to the sensory channels available in the stump or elsewhere (e.g., skin-stretch and electrotactile stimuli to skin mechanoreceptors and nerve free endings respectively); 6. Once learnt how to interpret the flow of afferent information, the user is able to infer size, shape and stiffness of the object held by combining, for example, the information relative to prosthetic hand aperture and force developed; 7. Such information can be used consciously or unconsciously to correct the new motor command (e.g., increase muscle contraction) without constantly looking at the device, thus freeing attentional resources.

Vibrotactile and electrotactile stimulation are among the most frequently used sensory substitution techniques (Antfolk et al., 2013; Kaczmarek, Webster, Bach-y-Rita, & Tompkins, 1991). Vibrotactile stimulation is delivered by means of a mechanical vibration applied directly to the skin of the subject. The parameters of the vibratory stimulus (i.e. frequency and amplitude) can be independently modulated to convey different kinds of information (Hasson & Manczurowsky, 2015a; Mann & Reimers, 1970; Witteveen, Droog, Rietman, & Veltink, 2012; Witteveen, Luft, Rietman, & Veltink, 2014; Witteveen, Rietman, & Veltink, 2015).

Single vibrators can be used independently or arranged in arrays, also giving the possibility to spatially encode the information to be delivered. Vibrators are usually low-power, unobtrusive and potentially embeddable within the prosthesis socket, worn upon the target stimulation area. Nevertheless, vibratory stimulation has several flaws, like habituation to the stimulus, which makes it barely perceivable after some time, and a low spatial resolution, because of its propagation to the surrounding tissues (Bark, Wheeler, Premakumar, & Cutkosky, 2008; Berglund & Berglund, 1970). Electrotactile stimulation involves an electric current delivered to the skin, inducing a local electric field that causes the afferent nerve endings to fire. It has many advantages, considering its stimulation parameters flexibility, the spatial resolution, and the small size of the available electrodes. However, the elicited sensation might turn into sharp and/or burning pain and thus need further calibration anytime the electrodes are replaced or even slightly displaced from their original location (Arakeri, Hasse, & Fuglevand, 2018; Dosen et al., 2017; Geng & Jensen, 2014; Paredes, Dosen, Rattay, Graimann, & Farina, 2015; Patel, Dosen, Castellini, & Farina, 2016; Schweisfurth et al., 2016; Štrbac et al., 2016).

Without proper precautions (e.g., intermittent stimulation to be preferred to continuous stimulation), even this type of stimulation could suffer from the effects of habituation (Buma, Buitenweg, & Veltink, 2007). Because of the absence of moving mechanical parts, electrotactile devices require less power and respond faster than vibrotactile ones, ensuring shorter delays of sensory restitution. The integration of electro- and vibro-tactile stimulation, delivered simultaneously at the same skin location, was also tested (D'Alonzo, Dosen, Cipriani, & Farina, 2014), providing an effective example of how more sensory channels can be synchronously involved, reducing the overall skin area needed to convey more information.

Haptic devices capable to stretch or provide pressure to the user skin were also employed to deliver proprioceptive information (Colella, Bianchi, Grioli, Bicchi, & Catalano, 2019; Rossi, Bianchi, Battaglia, Catalano, & Bicchi, 2019; Wheeler, Bark, Savall, & Cutkosky, 2010), either in homomodal or in heteromodal feedback restitution. Skin stretch devices are typically accurate, with a good intensity range and resolution, but are also heavy, cumbersome and energy consuming, hampering

their future integration in portable systems. Like vibrotactile devices, they suffer from a slow response of the system due to the mechanical inertia of the moving parts (Bark et al., 2008; Kaczmarek et al., 1991).

Beside touch, other sensory modalities have been exploited for sensory substitution, such as hearing or vision (Gonzalez, Soma, Sekine, & Yu, 2012). Due to the strong association between auditory and motor areas (Lezama-Espinosa & Hernandez-Montiel, 2020), sonification can be used to improve motor and proprioceptive performances (Castro et al., 2021a; Castro et al., 2021b; Cuppone, Cappagli, & Gori, 2019). Afferent information can be encoded by modulating the pitch, timbre or volume of individual auditory signals or by employing combinations of different tones (Earley, Johnson, Sensinger, & Hargrove, 2021). Auditory sensory substitution is light, fast, has low power-consumption, but it obviously interferes with normal hearing, is obtrusive and requires huge attentional resources. Another example of heteromodal sensory substitution is provided by augmented reality (AR) feedback, which allows to artificially increase the amount of visual information provided to the user by means of head-mounted displays or single-eye glasses as in (Clemente et al., 2017). Nevertheless, similarly to auditory sensory substitution, the interference with normal vision may become a limitation, not to mention the present need to wear additional devices on the face.

Proprioceptive homomodal restitution exploits muscle spindles and cutaneous mechanoreceptors to transmit information regarding the movements of a prosthesis to its user (Bark et al., 2008; Kayhan, Nennioglu, & Samur, 2018). Tendon vibration and skin stretch kinaesthetic illusions can be elicited both at larger joints like the elbow, as well as at the smaller interphalangeal joints (Collins et al., 2005; Pinardi, Raiano, Formica, & Di Pino, 2020b). However, while muscle spindles may remain after an amputation, such as the extrinsic muscles of the hand in transradial amputations, most of the times skin stretch must be delivered heterotopically (Bark, Wheeler, Lee, Savall, & Cutkosky, 2009), making the association between the feedback and the provided information less intuitive.

Control loops involving proprioception

In the following lines, studies investigating proprioception restitution in prosthetics and closely related fields are analysed, taking into consideration both the information extracted and encoded as well as the feedback strategy employed. The analysis addresses first the works involving only kinaesthetic senses of position and velocity, as well as configuration of the grip, followed by studies in which also force feedback was investigated, mostly focusing on grip strength. The studies reported were selected through a literature search that included proprioceptive feedback and non-invasive stimulation methods. The involvement of proper prostheses in the experimental design was not a strict criterion for selection and also preliminary investigations involving virtual end-effectors or surrogates

(e.g., cursors or lines on displays) were included given the pertinence to the topics and relative scarcity of works featuring a complete device. Although most participants involved in the studies were able-bodied subjects, some of the experiments described also included amputees.

Kinematic feedback: position, configuration and movement

Restitution of proprioceptive information regarding the position or the configuration of the prosthesis, as well as its movement, has been explored employing several feedback strategies (Figure 21). One of the earliest attempts to reconstitute proprioception showed improvement of positional control of the myoelectric Boston Arm, granted by the addition of a vibrotactile array display providing elbow angle information (Mann & Reimers, 1970). However, contrasting results were reported later: in able-bodied subjects the addition of position- or velocity-based vibrotactile feedback did not increase the rate of skill acquisition (i.e., relationship between movement velocity and accuracy) or improved task performances. In some cases, it was, indeed, detrimental, given the better performances (decreased error and movement time) reported following the removal of the additional feedback (Hasson & Manczurowsky, 2015b). More recently, similar performances between the vision-only and combined (vision + vibrotactile) feedback were reported, demonstrating that the vibration was not deteriorating the performances. However, the participants expressed, via the self-assessment workload evaluation NASA-TLX questionnaire, a 62.5% preference for the combined feedback, placing vision alone in second place (Guémann et al., 2022).

Vibrotactile stimulation arrays, mounted around the forearm of the participants, have been also employed for providing the degree of wrist prono-supination. A novel and customisable approach was described by the authors, employing a variable number of vibration motors and a flexible Gaussian interpolation-based intensity encoding algorithm, that allowed the subjects to achieve < 10% average error in target-achievement tests (Marinelli et al., 2023). Encouraging results were obtained when providing finger joint angle of a myoelectrical hand by means of a similar vibrotactile array mounted around the forearm of the user (Vargas, Huang, Zhu, & Hu, 2021).

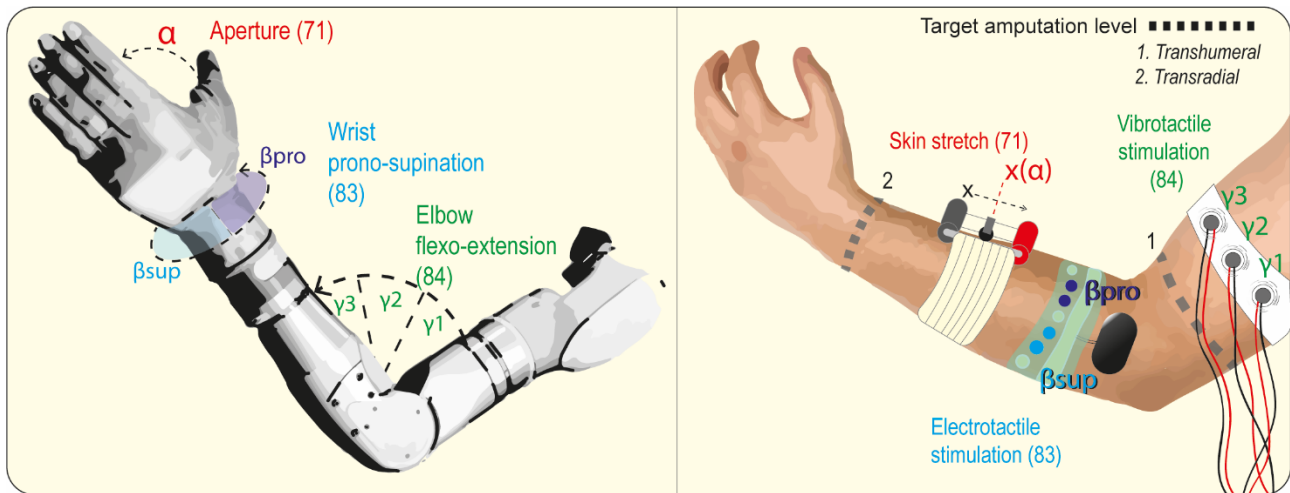


Figure 21, Examples of proprioception restitution strategies for coding positional and movement-related information. Stimulation devices have been illustrated as applied to a single limb to simulate their simultaneous use, but their choice will inevitably depend on the user's level of amputation and will therefore be tailored to the individual. The degree of grip aperture has been encoded into the movement of a skin-stretch stimulation device, whose position on the user's skin can be employed to infer the state of the prosthetic hand, thereby reducing the need for careful vision inspection (Rossi et al., 2019). Also, the prosthetic wrist's prono-supination state has been fed back by activating a dedicated combination of electrodes on the user's forearm (Garenfeld et al., 2020). Vibrotactile motors around the arm of the user have been used to encode discrete angular positions of the controlled myoelectric elbow (Guémann et al., 2022).

Electrotactile feedback also proved to be effective in returning proprioceptive information, even though vibrotactile stimulation was reported to provide better performances for hand opening feedback restitution in a virtual object grasping task (Witteveen, de Rond, Rietman, & Veltink, 2012). The delivery of hand aperture and wrist rotation feedback using a compact 16-channels electrotactile interface was tested during myoelectric control in thirteen able-bodied subjects executing a target-reaching task. Participants were able to correctly perceive and interpret the two independent channels of electro-tactile stimulation delivered closely and simultaneously, allowing them to use a myoelectric interface to move a cursor to the required targets on two degrees of freedom (DoF) (Garenfeld, Mortensen, Strbac, Dideriksen, & Dosen, 2020). In a more recent instance, subjects were able to correctly identify the degree of flexion-extension of a robotic hand prosthesis as well as its movement from one position to another taking advantage of the feedback provided by a forearm electrotactile array using spatial coding for providing both static and dynamic types of information. High success rates were reported for able-bodied subjects and 2 amputees taking part to the experiments (Han et al., 2023).

Individual fingers flexion level could also be encoded through electrotactile stimulation, allowing able-bodied subjects to reproduce a target level of flexion of either individual fingers or grips of a robotic hand actuated through myoelectric control. In this case, electrotactile feedback resulted to be better than no-feedback, but still, less useful than the visual-one (Patel et al., 2016).

Sonification has been employed in many motor control studies to improve proprioceptive performances, leveraging on intermodal learning and cross-modal processing (Bevilacqua et al., 2016), mostly dependent on the neuroanatomical interconnectivity between auditory and motor cortices (Ghai, 2018). When a properly tuned, auditory feedback was associated to a movement, such movements were learnt faster and performed better (Danna & Velay, 2017; Sigrist, Rauter, Marchal-Crespo, Riener, & Wolf, 2015). However, when sonification was specifically employed for proprioceptive sensory substitution, it yielded more modest results. Joint speed of a two DoF virtual hybrid positional-myoelectric prosthesis has been encoded by modulating the frequency of an auditory feedback. Such feedback of the EMG-controlled DoF improved target-position reaching performances only when a perturbed control was introduced to the task (Earley et al., 2021).

Several devices exploiting the skin stretch channel have been developed to restore proprioception, providing a complex combination of velocity, timing, and static force sense which subjects can use to map position of the tracked end-effector (Bark et al., 2009; Battaglia et al., 2017; Rossi et al., 2019; Wheeler et al., 2010). Positional feedback has been successfully provided in different settings, possibly implementing more DoF at the same time. A rotating skin-stretch device attached to the forearm was employed to encode positional information of a cursor's movement and better performances were reported compared to vibrotactile feedback (Bark et al., 2008). According to the authors, skin-stretch provided a more intuitive mapping for position information and a more realistic sense of velocity. In their following study, the same device was similarly used to convey feedback of a virtual object movement, in both active positioning and passive perception tasks. The subjects were able to map the feedback to the movement with minimal training, but poorer results were reported in the passive perception task, where the need of a higher level of concentration was reported (Bark et al., 2009). Angular position of a virtual EMG-driven prosthetic elbow was encoded into the magnitude of the provided skin stretch, leading to an overall improvement of the performance in a blind targeting task when compared to no-feedback control condition (Wheeler et al., 2010). Skin stretch can also be used to deliver more complex information using more than one actuator, e.g., rotation and translation of a robotic limb (Chinello, Pacchierotti, Bimbo, Tsagarakis, & Prattichizzo, 2018; Chinello, Pacchierotti, Tsagarakis, & Prattichizzo, 2016). A skin stretch tactor was designed to provide homomodal feedback about the three DoF wrist movements, based on the virtual angular position. Subjects were able to correctly identify the corresponding positions of the end-effector, even if prono-supination and ulnar-radial patterns of skin deformation, possibly similar, were sometime confounded (Kayhan et al., 2018). Skin stretch has been also successfully integrated with TVI to provide information about the ankle angle to a lower limb amputee (Shehata et al., 2019).

Skin-stretch feedback has been employed to convey information on hand aperture. No significant difference was shown between skin-stretch and vibrotactile feedback when participants were asked to classify six different hand configurations after a short training (Akhtar et al., 2014). Despite the similar performances, in the perspective of a prosthetic applications, the authors reported that their skin stretch device was more efficient in terms of power consumption, surface area occupied and weight. The Rice Haptic Rocker (Battaglia et al., 2017), an evolution of previously developed skin stretch devices (Chinello et al., 2018; Chinello et al., 2016; Liang et al., 2014), employs a rubber pad stretching the upper limb skin proportionally to the gripper aperture. The skin stretch feedback improved the performances in an object size discrimination test and provided feedback intuitive enough to not require significant dedicated attention. The device was also evaluated on a trans-radial experienced myoelectric prosthesis user who performed better on the Activities Measure for Upper Limb Amputees (AM-ULA) (Resnik et al., 2013), a measure evaluating task completion, speed, movement quality and skilfulness of prosthetic use. More modest results were reported in the passive size discrimination test (Battaglia et al., 2019). Promising results in discrimination tasks, both in able-bodied subjects and one amputee, were reported employing the Hap-pro, a similar device featuring a moving wheel on the user's forearm (Rossi et al., 2019). A further alternative is represented by the Stretch-Pro, which through the inward and outward rotation of one or two actuators allows a physiological-like deformation of the skin to be associated to movements. It outperformed the Hap-pro (85% vs 77% average accuracy) in the same discrimination task (Colella et al., 2019).

Kinetic feedback: addition of force

In a closed-loop control scheme, regulation of grasping force could benefit from proprioceptive-like feedback because visual clues are often not informative enough, even when constant visual monitoring is dedicated to the artificial hand.

There is still contrasting evidence about the benefits of providing hand force-related proprioceptive information through vibrotactile feedback. A study reported improved performances, where grip force feedback helped in reducing the effort of experimental subjects that were otherwise applying excessive and unnecessary forces in the vision-only condition (Pylatiuk, Kargov, & Schulz, 2006).

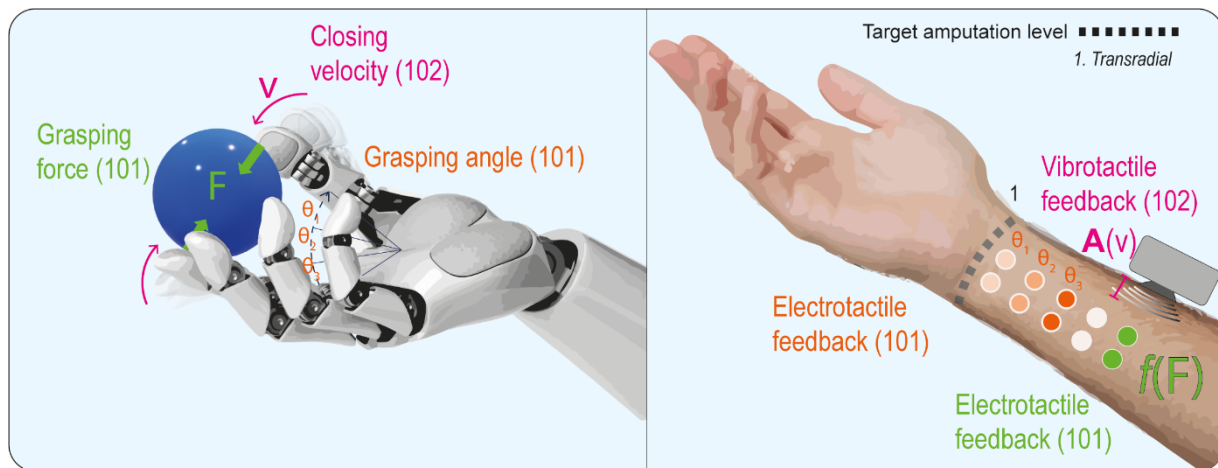


Figure 22, Examples of proprioception restitution strategies integrating both kinematic senses of position and movement and sensation of force. Stimulation devices have been illustrated all together, although the choices of the devices as well as eventual combinations must be tailored to the individual's needs. Electrotactile arrays can be used to provide different types of information by means of multiple encoding strategies: for instance, discrete grasping angles, corresponding to specific couples of electrodes on the user's forearm can be conveyed through spatial coding. Additionally, the frequency of the electrotactile stimulus provided by the last pair of electrodes can be proportionally adjusted to reflect the grasping force measured at the tips of the prosthetic fingers (Chai et al., 2019). Using a different approach, the amplitude of a vibrotactile stimulus on the user's forearm was set proportional to the grip's closing velocity (Ninu et al., 2014).

Vibrotactile feedback of force added to a virtual object manipulation task improved performances and decreased difficulty ratings with respect to control condition featuring only visual feedback (Stepp & Matsuoka, 2010). In further studies, force feedback was reported to be unhelpful, except for a few individuals more experienced with myoelectric prostheses (Chatterjee, Chaubey, Martin, & Thakor, 2008; Cipriani, Zaccone, Micera, & Carrozza, 2008).

A vibrotactile array on the forearm was employed to relay the single DoF of a virtual hand grip aperture and grasping force in able-bodied subjects and, later, in amputees (Witteveen et al., 2014; Witteveen et al., 2015). The use of this feedback allowed an improvement of grasping performances compared to no-feedback condition, but not compared to the condition when visual feedback was also available. A further study evaluated object manipulation performances after providing closing-velocity and grasping force, visually or through vibrotactile stimulation (Ninu et al., 2014) (Figure 22). Direct force feedback did not prove to be essential, since grip strength could be controlled predictively, estimating it from the closing velocity.

Electrotactile stimulation has also been used to return information about the force applied by a controlled device. Grasping performances of ten able-bodied subjects were tested in a virtual environment: two bipolar concentric electrodes, individually tuned according to perception and pain thresholds, delivered the same (either grasping or lifting) force information to participants who had to perform a virtual grasp and lift task using a joystick as a gated ramp controller (the type of control and feedback changed from grasping to lifting by pushing a button). Participants performed well also

in sessions with novel objects, demonstrating a successful skill learning and transfer (Jorgovanovic, Dosen, Djozic, Krajoski, & Farina, 2014). In another study, the force and grasping angle of a single-DoF myoelectric hand prosthesis were simultaneously encoded through spatial and intensity modulation of a five-channels electrode array stimulator, allowing able-bodied participants to discriminate 4 object sizes, 3 degrees of softness and 4 levels of grasping force (Chai, Briand, Su, Sheng, & Zhu, 2019). More complex information encoding has also been attempted. A compact multichannel electrotactile interface and a set of pre-programmed stimulation patterns were tested with the aim to translate aperture, grasping force and wrist rotations of a multi-DoF prosthesis (Štrbac et al., 2016). Tests were performed in ten able-bodied participants, and in 6 amputees to successfully prove the feasibility of this approach. The same research group tested the system in force control with routine grasping and force tracking tasks, using both a real and a simulated prosthesis in healthy subjects. Simultaneous spatial and frequency encoding obtained the best results in preliminary psychometric tests, proving to be the best method to reliably transmit up to 15 levels of high-resolution proprioceptive information. Results in the routine grasping task were similar between the benchmark visual feedback and the electrotactile feedback (Dosen et al., 2017).

Using augmented reality (AR) feedback, both proprioceptive information of grip closure and force of a robotic hand were provided by proportionally scaling the horizontal and vertical axes of an ellipse shown in the display (Clemente et al., 2017). Although such information was redundant and not strictly necessary to complete the grasping task, the addition of the AR feedback resulted in more consistent performances across the trials. Moreover, such feedback induced subjects to modify their behaviour (they scaled the grip force according to the modified corresponding axis of the ellipse), demonstrating the integration of the feedback into the sensorimotor dynamics.

Finally, an interesting alternative to force feedback is to provide the user with the information about the myoelectric system input, that is, the EMG activity itself. Performances were, indeed, improved when EMG feedback was added to force feedback both by decreasing force dispersion during routine grasping and increasing accuracy and stability in tracking the reference force profiles during a force steering task (Dosen, Markovic, Somer, Graimann, & Farina, 2015). A later work by the same group, compared the two types of information separately, conveyed through an electrotactile interface, and reported both an improved precision and decreased absolute error in the generation of grasping forces for the EMG feedback (Schweisfurth et al., 2016). EMG-feedback is anticipatory in nature, given that the input signal is generated much before the final output of the system (e.g., speed or force) and it gives the user time to adjust its behaviour, explaining the obtained results.

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Discussion & conclusion

The analysed studies do not highlight a best approach to provide non-invasive proprioceptive feedback. All the stimulation techniques described exhibit both pros and cons. On one side, homomodal feedback restitution (e.g., skin stretch) offers a more intuitive way of relaying information to the user, but there could be still some obstacles to the integration of these types of stimulators within prosthesis sockets (e.g., bulky size, high power consumption). On the other, heteromodal stimulation is less intuitive than homomodal techniques, but its broad applicability and cost-effectiveness, as well as the greater freedom to change stimulation features (e.g., independent modulation of amplitude and frequency of vibrotactile and electrotactile stimulation, the possibility to arrange multiple stimulators in arrays), make it a valuable option for feedback restitution. Also, it may be argued that heteromodal proprioception restitution takes advantage of predominantly

exteroceptive sensory channels (e.g., skin mechanoreceptors and nerve free endings). However, proprioception and exteroception are intertwined, and the boundary between the two is blurred, with information from multiple receptors being integrated at multiple levels. We can perceive the external world through our proprioceptors (e.g., translating the configuration of the hand into the size of a grasped object), and skin mechanoreceptors have a dual nature, providing information about both movement and contact forces. Therefore, as long as the sensory stimulus can be translated into meaningful information regardless of the input channel, heteromodal stimulation should be considered as valuable as the homomodal counterpart (Thomas, Ung, McGarvey, & Brown, 2019). Regarding the results obtained with each stimulation techniques, there is evidence to support the use of vibrotactile feedback for the restitution of proprioception. More accurate performances, compared to other feedback conditions, were reported when relaying both hand configuration and grip force (Cipriani et al., 2008; Pylatiuk et al., 2006). Skin stretch stimulation, also, appears to be a reliable way of proprioceptive information transfer, providing more consistent and unambiguous results (Bark et al., 2009; Battaglia et al., 2019; Rossi et al., 2019). Beside the more intuitive nature, the association between movement and a skin stretch stimulation may be more direct since both can be generally described with a modulus (stimulus intensity) and a direction.

Electrotactile feedback has proven to be another viable alternative for proprioceptive feedback restitution. Many channels can be placed on a limited surface, as the one of the amputee stump, and more advanced coding schemes can be employed (Dosen et al., 2017). This likely allows to deliver more types of information simultaneously, a convenient feature for the restitution of proprioception that is composed of multiple types of information merged together. Still, care should be taken to electrodes repositioning and all the issues related to changes in perception and pain thresholds (Boljanić et al., 2022). Both AR and auditory proprioceptive feedback need further development and refinement to go beyond research settings. They interfere with normal sight and hearing and may require the user to devote non-negligible attentional resources, unlike normal proprioception which contributes to motor control in a mostly unconscious way. While it is true that other types of stimulation would similarly require the user's attention, peripheral input channels (e.g., the skin of the stump) are not at risk of being saturated with information as central senses such as sight and hearing are.

Furthermore, it should be noted that different types of stimulation strategies may vary in their suitability for restoring proprioception in multi-articulated prostheses. Each strategy exhibits varying levels of efficiency in handling different numbers of DoF. Electrotactile arrays have the advantage of compactly encoding a larger amount of information related to multiple degrees of freedom within a limited space compared to other devices like skin stretch devices. The latter, despite the higher energy

requirements, could indeed perform better in single-DoF scenarios, given, for example, the greater familiarity of subjects with the stimulation, but it may no longer be optimal for multiple-joint/DoF control.

Skin receptors serve as the primary pathway for information transmission in most sensory substitution approaches. In the case of amputees, the availability of tissues may vary, but it remains evident that targeting regions with the highest density of receptors, thus providing the highest resolution for perception, would be the most straightforward strategy. This can be considered true regardless of the specific type of information being encoded. In humans, beside the face whose stimulation would be invasive and impractical, such high density is found distally along the limbs, with the highest found in the skin of the hands and fingers, which, in most amputation cases requiring the use of a prosthesis, is absent. Therefore, in the literature, the remaining tissues of the upper limbs (e.g., forearm and arm), represent the preferred choice for sensory substitution studies (Antfolk et al., 2013). Moreover, it can be speculated that the proximity between the source of sensory information and the muscles controlling the end effector to which the information pertains facilitates the sensorimotor integration required for optimal control of the latter. This is due to the somatotopic cortical organisation which plays a role in enabling sensorimotor integration, that, indeed, relies on intraareal neuronal coherence (Arce-McShane, Ross, Takahashi, Sessle, & Hatsopoulos, 2016), which has been shown to depend on the spatial reach (Myers et al., 2022). In case of homomodal stimulation (e.g., TVI), the localisation strategy must be dictated by the type of perception you want to elicit. It is worth also considering that, beside the location, also the preferred pattern of stimulation may vary among different subjects. For amputees, this will be also affected by the remaining tissues of the stump, both in terms of quantity and quality of innervation. It is therefore fundamental to be able to adjust such patterns on a patient-specific basis (Sagastegui Alva, Muceli, Farokh Atashzar, William, & Farina, 2020).

Further technological development of the hardware (e.g., reduced dimensions, lower power consumption, better performing encoding algorithms) is likely necessary to achieve a completely satisfactory feedback strategy. However, more tools to investigate all the effects deriving from the additional feedback are needed to help define such a degree of satisfaction. Thus, to this aim, in the following paragraphs some considerations are made on the possible aspects of proprioception restitution to be investigated.

When evaluating the effects of an additional feedback, two strategies can be adopted, one after the other or in parallel: i) single-modality evaluation; in the preliminary phases of developing a restitution strategy for a specific sensory channel, it may be beneficial to separately evaluate the contribution of individual feedback modalities (e.g., vision, hearing, natural/artificial proprioception etc.); ii)

integrated evaluation; considering that the aim of feedback restitution is the improvement of the prosthesis' control in real life, the experimental settings should also allow to simulate and evaluate the effects of the ecological integration of multisensory information. It is important to consider that some advantages of the added feedback may be intangible in one case, but extremely significant in the other and *vice versa*.

In most of the reviewed works, however, the artificial feedback (e.g. vibrotactile) was only compared to a no-feedback condition (Mann & Reimers, 1970; Wheeler et al., 2010) and in the few cases where the addition of proprioception to vision was tested, performance did not improve (Pistohl, Joshi, Ganesh, Jackson, & Nazarpour, 2015). There are at least two potential reasons for this: i) ceiling effect, i.e., the experimental task is so easy that visual supervision is enough to execute it at its best, and thus, more ecological tasks are needed, designed so that their effective completion requires rich and multimodal adaptive behaviours; ii) need for longer training. Indeed, the advantages of the added feedback might not be evident after a short learning phase. Humans are accustomed to experience the environment and its unpredictability through vision, relying predominantly on it (Ernst & Banks, 2002; Pavani et al., 2000; Shadmehr & Krakauer, 2008; Sober & Sabes, 2005) so that integrating the new artificial feedback into the sensorimotor dynamics, as well as learning how to properly use it, may likely require a long time. Once accustomed to the new feedback, the relative weight of the proprioceptive information in building the motor command should increase and influence the performances (Ernst & Banks, 2002). In a few studies where the users were given enough time to train and learn, performances over multiple sessions were indeed improved by the proprioceptive feedback (Clemente et al., 2019; Stepp, An, & Matsuoka, 2012). Furthermore, as the subjects' ability to determine relevance and effectively utilise new information improves, their perception of the stimulus itself has also been demonstrated to enhance through training. For instance, training has led to improvements in the detection of subtle intensity differences, resulting in a more effective transfer of information, given the increased resolution of perception (Stronks, Walker, Parker, & Barnes, 2017).

Nevertheless, the potential enhancement of real prosthetic device control through the incorporation of proprioceptive sensory feedback systems may vary. Existing literature suggests a significant improvement compared to complete feedback deprivation. The regularity in a prosthetic device's operation across various activities is an additional key factor to consider when gauging its control quality. Indeed, restoring proprioception has been shown to reduce the variability in the device's performance (Blank, Okamura, & Kuchenbecker, 2008). Moreover, while vision plays a dominant role in simple tasks involving a single degree of freedom, the coordination of multi-joint movements

is more likely to rely on proprioceptive inputs for efficient control (Sainburg, Poizner, & Ghez, 1993) and, therefore, proprioceptive feedbacks for the actuation of more complex prosthetic devices.

Proprioceptive feedback, beside improving motor control, has also the potential to enhance the embodiment of the prosthesis, a complex, multi-componential process referring to the sense of owning and controlling our own body parts, whether real or artificial (Longo, Schüür, Kammers, Tsakiris, & Haggard, 2008). Embodiment builds up from the inter-sensory congruency of stimuli (de Vignemont, 2011), which could be further enhanced by the similarly congruent addition of proprioceptive feedback. The artificial feedback can be congruent with the visual feedback coming from the moving end-effector to be embodied (Dummer, Picot-Annand, Neal, & Moore, 2009; Walsh, Moseley, Taylor, & Gandevia, 2011), as well as with the efferent motor command (i.e., efference copy) that can be treated itself as an additional sensory modality (Pinaridi et al., 2020a). Considering that the myoelectric control of a device contributes to its embodiment (Niedernhuber, Barone, & Lenggenhager, 2018), supporting the role of visuomotor congruency in its induction (Kalckert & Ehrsson, 2012), we hypothesise that further enriching the visual feedback with proprioception would provide a collateral ownership-boosting congruence, likely beneficial to the device acceptance. Hitherto, in prosthetics, the effects of proprioceptive feedback on embodiment has not been investigated as extensively as, for instance, the addition of touch (D'Alonzo, Clemente, & Cipriani, 2015; D'Alonzo et al., 2014; Di Pino et al., 2020a; Ehrsson et al., 2008; Page et al., 2018). To the knowledge of the authors, a limited number of works studied the embodiment together with motor performances, but promising results were obtained using peripheral nerve stimulation providing both touch and kinaesthetic sensations (Schiefer, Tan, Sidek, & Tyler, 2015), and by using the TVI in amputees who underwent nerve-transfer surgery (Marasco et al., 2021) (Targeted Muscle Reinnervation, i.e., surgery involving the transfer of motor and sensory nerves from the stump to remaining functional body parts in order to use the latter to amplify motor signals and feed them into myoelectric interfaces (Kuiken et al., 2009).

Acceptance of the prosthesis depends also on its ease of use, considering both physical and mental effort. So far, addition of sensory feedback was mostly discussed in terms of performance improvement but, when assessing its usefulness, motor performance may not reflect the complete experience of the amputee. Controlling a prosthesis that does not provide feedback on its configuration and motion requires the user to devote continuous visual contact to its operation, with a consequent burden of attentional resources. One of the purposes of additional feedback should be precisely, when performing any task, to reduce the required cognitive load (i.e., a measure of the total amount of mental effort that an individual must exert in order to complete a task, including both the effort required to process new information and the effort required to maintain that information in

working memory (Sweller, van Merriënboer, & Paas, 1998). For instance, in a simple cup transfer task the addition of kinaesthetic feedback allowed the subjects to "trust" the prosthesis more, thus influencing the time-percent fixation to the hand and to the target, resulting in a control behaviour and attentional commitment closer to the one of able-bodied subjects (Marasco et al., 2021). Vibrotactile feedback relaying the force exerted by a myoelectric prosthesis, compared to a no-feedback condition, led to a reduction of the haemoglobin concentration in the right medial prefrontal cortex measured with functional near-infrared spectroscopy (fNIRS), suggesting a reduced mental effort needed to operate the device (Thomas, Ung, Ayaz, & Brown, 2021). Further physiological parameters, like encephalic and cardiac electrical activity (EEG, ECG), electro-dermal activity (EDA), and respiration rate, were also shown to be good predictors of the cognitive load associated to manipulation tasks (Gonzalez et al., 2012), and could serve our purpose.

Methods to assess brain plasticity resulting from proprioception manipulation could further support behavioural results with more objective and quantifiable parameters. Proprioceptive feedback, indeed, especially when it is experienced along a training period, is able to modulate brain motor (Avanzino et al., 2014; Macé, Levin, Alaerts, Rothwell, & Swinnen, 2008) and somatosensory (Carel et al., 2000) functioning. Components of somatosensory evoked potentials (SEPs) have been suggested as indices of proprioceptive afferences (Mima et al., 1996; Restuccia et al., 2002; Seiss et al., 2002; Valeriani et al., 1996) and could be used as evidence of the artificial input's influences on cognitive processes. Furthermore, internal models are continuously updated by proprioceptive inputs (Wolpert, Miall, & Kawato, 1998) and provide the starting point for motor planning. Motor evoked potentials (MEPs) are a suitable indicator of the dynamic changes occurring during the preparation of an action (Bestmann & Duque, 2016) and could therefore represent a tool to objectify the effects of artificial proprioception on motor behaviour.

Lastly, due to the easiness of recruitment and the need to avoid the premature involvement of patients to test preliminary hypotheses, most of the analysed studies on sensory substitution have been conducted on able-bodied subjects. Studying healthy subjects is extremely useful, but the generalisation of the results to amputees should be approached with extreme care, especially because of the plastic phenomena affecting amputees' brain (extensively covered elsewhere e.g., (Di Pino et al., 2009; Makin, Scholz, Henderson Slater, Johansen-Berg, & Tracey, 2015). Plastic changes of their sensorimotor circuits, believed to be at the basis of the phantom limb pain (PLP), are particularly relevant for the study of sensory substitution (Di Pino, Piombino, Carassiti, & Ortiz-Catalan, 2021; Flor, Nikolajsen, & Staehelin Jensen, 2006). PLP is the sensation that the lost part is still present and painful, experienced by most amputees (Stankevicius, Wallwork, Summers, Hordacre, & Stanton, 2021). Several cues suggest that proprioception has a key role in PLP (Anderson-Barnes, McAuliffe,

Swanberg, & Tsao, 2009b; Giummarra, Gibson, Georgiou-Karistianis, & Bradshaw, 2007a; Ramachandran & Hirstein, 1998b). While some amputees can move their phantom at will, in the majority of cases the phantom is locked or frozen in fixed positions usually resembling the position of the limb just prior to the amputation. This has been interpreted as the result of some kind of persisting “proprioceptive memory” (Anderson-Barnes et al., 2009b). The contribution of proprioception in PLP is also suggested by Ramachandran and Hirstein (1998), whose foundational work proposed a mismatch between visual and proprioceptive inputs as a major contributor to the syndrome and provided the rationale for “mirror therapy” (Barbin, Seetha, Casillas, Paysant, & Pérennou, 2016). Indeed, mirror therapy aims at artificially restoring the congruency between visual feedback (the reflection of the healthy limb), the copy of the produced motor command (the efference copy) and the proprioceptive re-afferents (due to stump muscles' activation). With the same purpose, vision can also be tricked with an healthy-looking limb through videos and Virtual/AR (Ortiz-Catalan, Sander, Kristoffersen, Håkansson, & Brånemark, 2014). The improvement of PLP and the reduction of abnormal cortical plasticity after a long-term use of myoelectric prosthesis (Lotze et al., 1999) is likely based upon the same rationale. The lack of the congruent proprioceptive information from the artificial limb that the user controls and sees could represent a defective opening within the ideal closed loop of prosthetic motor control that deserves to be further investigated in the future. In light of the preceding discussion, beside the integration of the device in the body schema of the user (see paragraph on Embodiment), care should be taken, whenever the recruitment makes it possible, to the effects of artificial proprioception on cortical plasticity and phantom limb phenomena (Giummarra et al., 2007a), since both have been shown to depend heavily on multisensory congruence.

8 Conclusions and outlook

8.1 Aim

The aim of this thesis is to provide a comprehensive overview of the body representation and its alterations, whether they result from a medical condition or are experimentally induced, and to contribute to the understanding of the phantom limb pain phenomenon. In this work, I have had the opportunity to delve into how the concept of body representation is multifaceted. The literature in this field is extensive, but in some cases, due to the different approaches through which it has been observed and the various terminologies employed, also confusing. However, such diversity does not necessarily represent a weakness. On the contrary, it offers diverse perspectives from which we can strategically plan, for example, new pain management interventions.

To address this challenge, the concept of embodiment becomes crucial in connecting amputees with their artificial limbs. Embodiment refers to the experience of ownership and agency over a corporeal entity, and it is essential for recovering the representation of the body. Multisensory integration and sensorimotor plasticity play significant roles in enabling embodiment, allowing the brain to adapt to changes in sensory inputs and improve brain connectivity.

In this scenario, understanding the layered structure of body representation, the role of vision and proprioception, and the how to provide sensory feedback provides valuable insights for managing the consequences of limb loss and designing interventions to restore full functionality in amputees.

8.2 Major contributions and findings

Body representations has a stable component

In the past, the existence of a canonical and predetermined body posture that impacts sensorimotor functions had already been hypothesised (Bromage & Melzack, 1974a). Supporting recent research (Romano et al., 2017; Romano et al., 2021; Romano et al., 2019), we have confirmed the hypothesis that there exists a preferential postural representation of the hand and revealed its physiological origin using Transcranial Magnetic Stimulation (TMS). This has allowed us to highlight that the cortical circuit involved in the computational advantage includes the ventral Premotor (PMv) and primary motor (M1) cortices, providing us a neural substrate responsible for facilitating the subject's interaction with the environment through the so-called standard hand posture. In our view, this posture is a heritage of phylogenetic development, emphasising that body representation has a

predetermined and stable component over time. Understanding the brain circuits responsible for the standard posture could offer new potential targets for therapeutic interventions in prosthetic and rehabilitative contexts. Future studies could focus on enhancing this network to support motor relearning following prosthetic integration. Leveraging the stable component of hand representation, for example, by promoting connectivity between PMv and M1 through brain stimulation, could facilitate the interaction of the new limb with the environment.

Body representation can be artificially re-shaped

On one hand, the brain contains information inherited from our ancestors that remains stable over time. On the other hand, the representation of our body can be relatively modified in response to externally induced perceptual changes. In the second study, a Virtual Hand Illusion (VHI) paradigm was used with an elongated forearm in a first-person perspective to induce the illusion of owning an elongated forearm. By comparing different conditions, including varying levels of elongation magnitude and synchronicity of VHI, it emerged that the brain rescales the perceived distance between two points based on the observed dimensions of the body. An interesting result of this study was the fact that the perceived increase in the distance was related to the elongation but not to the synchronicity. This suggests that virtual experience may be more related to the vision rather than to the multisensory integration. This finding could be valuable when considering the study of modifications of body image through virtual reality, as it suggests that body representation may be influenced differently using this approach compared to when standard RHI protocols are employed. Moreover, the rescaling process emerged solely in the tactile task which was related to exteroception. Differently, the lack of body representation modification in the proprioception suggests that, although proprioception and exteroception are intertwined, the two senses may differently respond to the visual feedback modification.

Altered body representations after amputation result in phantom limb pain

As already discussed, body representation can undergo several changes. In the previous experiment, artificially induced changes were demonstrated, but in some pathological phenomena, the alterations that occur can become a medical issue. Phantom Limb Pain (PLP) is one of the most common sequelae of amputations, representing a widely misunderstood phenomenon often attributed solely to psychological factors. Contemporary understanding suggests PLP results from complex interactions between structural and functional changes both in central and peripheral nervous system. In our review, we have examined various physiological models. While peripheral pathogenesis such as neuromas (Collins et al., 2018), unwanted discharges from somatosensory receptors (Campbell et al.,

1989) and vascular changes in the stump (Sherman & Bruno, 1987) have been attributed more often to the neuroma pain, phantom limb pain has been linked to more massive modifications.

For instance, central models, such as remapping model and persistent representation model focus on brain plasticity mechanisms after the lesion and postulate two opposing mechanisms. The first explains the pain through cortical reorganisation (Flor et al., 1995) in which connections from adjacent areas to those of the lost limb expand and invade it, while the second (Makin & Flor, 2020) hypothesises that the pain is generated by the maintenance of the representation of the lost limb and the continuous sending of input to it. Although we do not report here all the models analysed in the chapter, our key conclusion is that they may not be mutually exclusive for several reasons. First, stump pain caused by peripheral damage can occur individually or coexist with phantom limb pain. Second, partial cortical reorganisation may occur where a portion of the limb is still well represented. Third, pharmacological and non-pharmacological treatments have highly variable efficacy and are subject-dependent. This suggests that different treatments may act on different characteristics of the phenomenon and likely different causes. Therefore, it could be asserted that we are dealing with a multifaceted phenomenon characterised by diverse features, amenable to investigation from various perspectives, and that an effective treatment should address it comprehensively, targeting each of these facets in a tailored fashion.

Pain may be influenced by body image

Previously, it has already emerged that visual feedback has the greatest modulatory impact on body representation. In the paragraph concerning changes in tactile perception through virtual reality, it was emphasised that the illusion primarily occurred through vision. By exploiting this property of visual feedback, our aim here was to provide experimental data to support the hypothesis that one of the causes of phantom limb pain is the discrepancy between sensory feedback from the residual limb after amputation and the pre-existing body representation. Although our artificial model is complex, and the results should be interpreted with caution as they come from a simulation in a virtual environment, they can provide an interesting starting point for a deeper understanding of the phenomenon. We observed that the vision of an altered body image and the associated discomfort may exacerbate the pain perception and affect the autonomic response. In line with our model, it appears that the cause of pain may be not the absence of visual feedback itself, but rather the inability to identify the source of pain and the sight of one's own body image altered. These results support the idea of restoring body representation and consequent pain reduction through the embodiment of the prosthesis. One might argue against this hypothesis by saying that patients can still attribute the cause of pain to the residual limb. However, patients with phantom limb pain perceive the pain on the

phantom limb and not just on the residual limb, or at least not exclusively. A well-integrated prosthetic limb might represent a source of pain and likely reduce it, as seen with mirror therapy. Additionally, reconstructing one's own body image would allow the patient to reduce the discomfort associated with it, which, as observed, contributes to an increased pain response.

Incorporating non-invasive proprioceptive feedback strategies is imperative for the recovery of various aspects of body representation, but there is no one-size-fits-all approach

Prosthetic limbs may engage the brain regions typically associated with the hand representation, particularly in individuals who use them regularly. The use of prostheses appears to influence the reconfiguration of the brain, fostering stronger connections between visual and sensorimotor areas (van den Heiligenberg et al., 2018). Proprioception in phantom limb pain has been previously investigated by different viewpoints emerging as a crucial point. Some authors argue that phantom sensations result from the proprioceptive memory of the arm's position associated with pain before amputation (Anderson-Barnes et al., 2009a), while others attribute them to the incongruence between visual and proprioceptive feedback from the limb (Ramachandran & Hirstein, 1998a). It is evident, therefore, that restoring vision-proprioception congruency, may be essential for improving prosthesis control and allowing recovery of the altered body representation.

After reviewing various methods for non-invasively providing proprioceptive feedback, we have concluded that there is no definitive and superior approach. However, advantages and disadvantages of the various methods emerged can guide the choice. For instance, homomodal feedback restitution is certainly more intuitive in providing information but, at times (i.e., skin stretch), it can be more cumbersome. In contrast, heteromodal stimulation, such as electrical stimulation, is more practical and flexible. The type of feedback (vibrotactile, electrical, auditory...) is differently efficient when used to convey information related to configuration, position, or force. Performance may also depend on the stimulation site, the number of degrees of freedom provided, and the combination of multiple types of feedback simultaneously. The latter raises curiosity because, although in a physiological situation we typically integrate information from various senses, allowing for seamless interaction with the environment, in an experimental setting it seems that the addition of proprioceptive feedback does not always improve performance compared to when only visual feedback is used. This confirms the dominant role of visual feedback. However, the utility of proprioceptive feedback may depend on the type of performance required and, in any case, it has a potential effect on embodiment, which, as mentioned earlier, can alleviate pain.

8.3 Conclusive framework

Starting from the exploration of the stable component of body representation, we have highlighted the role of the PM cortex in the computational advantage of hand posture. This inherent predisposition to facilitate interaction with the environment, elucidating a cortical network, provides intriguing insights for motor rehabilitation applications. Alongside these evolutionarily acquired characteristics of body representation, we have also investigated its short-term plasticity. In the second experiment, we demonstrate that perceptual changes can be induced by a virtual manipulation of body representation. The possibility that the latter also exhibits plastic features prompts us to investigate its role in phantom limb pain, a classic example of pathological alteration of body representation. Examining this phenomenon in all its neurophysiological components has led us to propose a multifactorial model facilitating a better differential diagnosis (e.g., between neuroma pain and phantom limb pain), consequently enabling targeted pain management. Simultaneously, the model has revealed the role of changes (i.e., lack of sensory feedback) in body representation in pain, guiding us to the subsequent experiment. Through the study of visual feedback in pain modulation, we have highlighted the role of certain altered visual factors and the discomfort associated with the alteration of body image in the painful experience, both in its subjective component and autonomic responses. Emphasising the primary role of pain source localisation in phantom limb pain provides insights into the importance of restoring visual feedback and its congruence with the proprioceptive one. This suggests the necessity of identifying sensory feedback restoration strategies to enable patients to receive appropriate prosthetic treatment. To achieve this goal, we have delved into proprioceptive feedback restoration strategies, concluding that, similar to the findings from the phantom limb model, there is no one-size-fits-all strategy, and each case should be studied in detail with an individual-centered approach considering the advantages and disadvantages of each technique.

8.4 Future works and open questions

In this thesis work, we have extensively analysed how body representation can be altered and how its plasticity can represent both an advantage and a disadvantage. Exploring the impact of visual feedback has provided us with a way to conceptualise a different explanation of phantom limb, which, although intriguing, remains incomplete. While we have been able to study the impact of body image on pain by manipulating it, we have not yet done the same with proprioception. Identified the role that poor visibility of the hand, altered arm length, and the presence of the injury, as well as the

discomfort associated with them, have on pain, future work should focus on the interaction of these factors with also altered proprioception. Several tools come to our aid to induce modulation of proprioceptive feedback, the foremost being the tendon vibration illusion (TVI), which, by applying vibration at a certain frequency to the biceps or triceps tendon, induces an illusory sense of movement in subjects (Goodwin et al., 1972). In the context of refining the model, not only would a double modulation be considered with the aim of reproducing a more vivid visuo-proprioceptive incongruence in healthy subjects, but it could better mimic neuropathic pain by using a thermal grill that induces illusory pain caused by simultaneous hot and cold thermal stimulation (Bouhassira, Kern, Rouaud, Pelle-Lancien, & Morain, 2005; Li, Petrini, Wang, Defrin, & Arendt-Nielsen, 2009; Shin & Chang, 2021). Investigating the physiological response to illusory pain through more specific techniques such as Pinprick evoked potentials (PEPs), or Laser evoked potentials (LEPs) would allow the study of central sensitisation phenomena in healthy subjects contributing to a further understanding of PLP.

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